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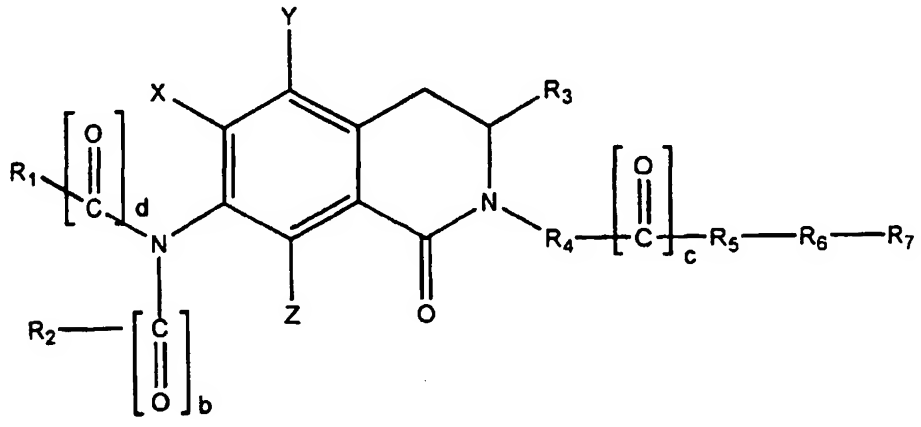
(54) Title: 4-UNSUBSTITUTED DIHYDROISOQUINOLINONE DERIVATIVES AND COMBINATORIAL LIBRARIES THEREOF



(I)

(57) Abstract: The present invention relates to novel dihydroisoquinolinone (DHQ) derivative compounds of formula (I): wherein R_1 to R_7, X, Y, Z, b, c and d have the meanings provided herein. The invention further relates to combinatorial libraries containing two or more such compounds, as well as methods of preparing DHQ derivative compounds.

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4-UNSUBSTITUTED DIHYDROISOQUINOLINONE DERIVATIVES AND COMBINATORIAL LIBRARIES THEREOF

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention relates generally to the synthesis of compounds comprising heterocyclic rings. In one specific embodiment, the invention provides novel 4-unsubstituted dihydroisoquinolinone ("DHQ") derivative compounds as well as novel combinatorial libraries comprised of such compounds.

BACKGROUND INFORMATION

The process of discovering new therapeutically active compounds for a given indication involves the screening of all compounds from available compound collections. From the compounds tested, one or more structures is selected as a promising lead. A large number of related analogs are then synthesized in order to develop a structure-activity relationship and select one or more optimal compounds. With traditional "one-at-a-time" synthesis and biological testing of analogs, this optimization process is long and labor intensive. Adding significant numbers of new structures to the compound collections used in the initial screening step of the discovery and optimization process cannot be accomplished with traditional "one-at-a-time" synthesis methods, except over a time frame of years or even decades. Faster methods are needed that allow for the preparation of up to thousands of related compounds in a matter of days or a few weeks. This need is particularly evident when it comes to synthesizing more complex compounds, such as 4-unsubstituted DHQ derivative compounds.

Combinatorial approaches have recently been extended to "organic," or non-peptide, libraries. For example, Zambias et al. (U.S. Patent No. 5,712,171) describe a method of generating libraries that contain aminimides, oxazolones, sulfonylaminides and phosphonylaminides as the core structure in spatially arranged arrays. Combinatorial chemical methods have been applied to a limited number of heterocyclic compounds, as described, for example, in Wilson et al., *Molecular Diversity*, 3:95-112 (1998); U.S. Patent Nos. 5,288,514; 5,324,483; and Goff et al., *J. Org. Chem.*, 60:5748-5749 (1995). See also U.S. Patent Nos. 5,549,974 and 5,506,337. However, the heterocyclic libraries to date contain compounds of limited diversity and complexity.

Substituent limitations have been overcome for mixtures of peptides and peptidomimetics through the use of solid phase techniques versus solution-phase. An important step in the development of solid-phase techniques was the discovery of methods to prepare large numbers of individual compounds simultaneously, as described, for example, by Houghten in U.S. Patent No. 4,631,211. These solid phase methods, however, have rarely been applied to the syntheses of complex heterocyclic structures. Therefore a need exists to develop more complex "organic" libraries based on heterocyclic medicinal compounds which would need less time and effort in the synthesis and testing required to bring an organic pharmaceutical product to fruition. In short, improved methods for generating therapeutically useful heterocyclic compounds, such as 4-unsubstituted DHQ derivatives, are desired.

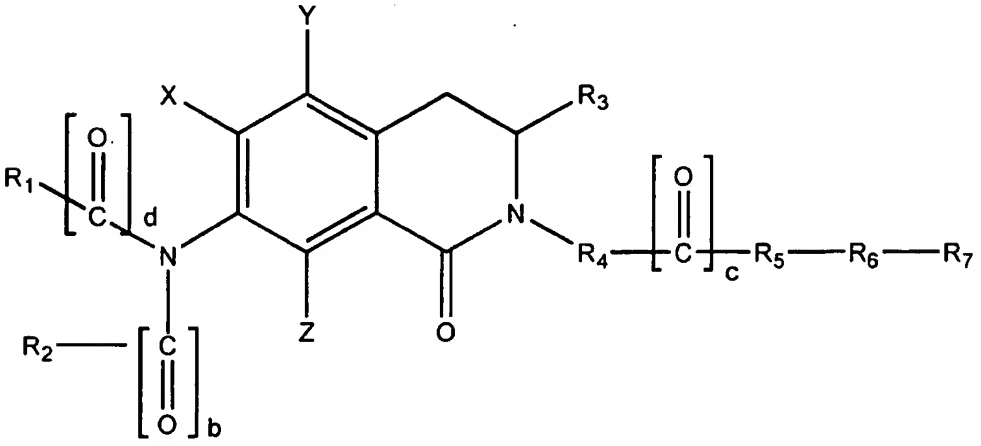
DHQ derivative compounds have been the subject of investigation in a number of different biological areas. For example, DHQ derivatives have been proposed as useful: (a) as 5-hydroxytryptamine receptor agonists (U.S. Pat. No. 5,491,148) ; and (b) in treating cancer (Suto et al., *Anti-Cancer Drug Design*, 7:107-117 (1991)). DHQ derivatives have also been the subject of serial chemical synthesis. See, for example, Haimova et al., *Tetrahedron*, 33:331-336 (1977). However, more complex DHQ derivatives, especially those unsubstituted at the 4-position and, even more especially, those also with amino or amido substitutions at the 7-position, have been difficult to attain.

This invention satisfies this need and provides related advantages as well. The present invention overcomes the known limitations to classical serial organic synthesis of DHQ derivatives, for example, as well as the shortcomings of combinatorial chemistry related to DHQ derivatives. The present invention allows for rapid generation of large diverse libraries of complex DHQ derivatives as discrete molecules or molecules bound to solid support, such as a resin. The present invention can utilize a readily available pool of building blocks that can be incorporated into the various regions of the molecule. Furthermore, the method of making the present invention allows for the use of building blocks that contain a wide range of diverse functionality. Such building blocks can provide combinatorial libraries that consist of large numbers as well as combinatorial libraries that are extremely diverse with respect to the functionality contained within those libraries. The present invention combines the techniques of solid-phase synthesis of DHQ derivatives and the general techniques of synthesis of

combinatorial libraries to prepare highly diverse new DHQ derivative compounds.

SUMMARY OF THE INVENTION

The present invention relates to novel DHQ derivative compounds of the following formula:



wherein R_1 to R_7, X, Y, Z, b, c and d have the meanings provided below.

The invention further relates to combinatorial libraries containing two or more such compounds, and to methods of generating DHQ derivative compounds.

BRIEF DESCRIPTION OF THE DRAWINGS

In Figures 1 to 4, described below, as well as the examples, $-NR_1-$ (not shown in Figures 3 and 4) corresponds to R_5 of the claimed invention (which can be $-NR_{12}-$); R_2 corresponds to R_3 of the claimed invention; and R_3 corresponds to R_2 of the claimed invention.

Figure 1 shows the reaction scheme for the combinatorial synthesis of DHQ derivative compounds with

a) 1,2-ethylene at the R_4 position of the claimed invention; and b) $-NR_1-$ shown in Figure 1 corresponding to R_5 of the claimed invention, which is $-NR_{12}-$.

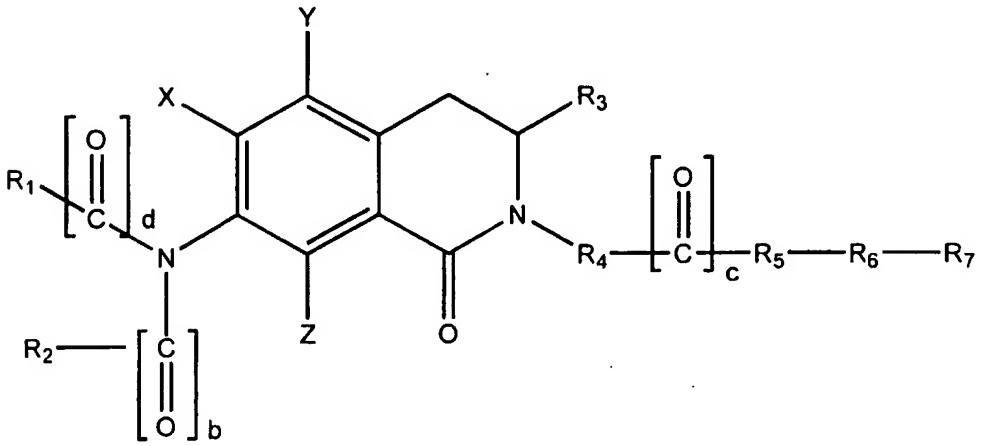
Figure 2 shows the reaction scheme for the combinatorial synthesis of DHQ derivative compounds with a) the formula D-W-E at the R_4 position of the claimed invention, where D is directly attached to the DHQ nitrogen and is methylene, W is phenylene and E is absent; and b) $-NR_1-$ shown in Figure 2 corresponding to R_5 of the claimed invention, which is $-NR_{12}-$.

Figure 3 shows the reaction scheme for the combinatorial synthesis of DHQ derivative compounds with a) 1,2-ethylene at the R_4 position of the claimed invention; and b) -O- at the R_5 position of the claimed invention.

Figure 4 shows the reaction scheme for the combinatorial synthesis of DHQ derivative compounds with a) the formula D-W-E at the R_4 position of the claimed invention, where D is directly attached to the DHQ nitrogen and is methylene, W is phenylene and E is absent; and b) -O- at the R_5 position of the claimed invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides novel compounds and combinatorial libraries of novel compounds of the formula:



wherein:

R_1 and R_2 are, independently, a hydrogen atom, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, C_2 to C_{12} alkenyl, C_2 to C_{12} substituted alkenyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, C_1 to C_{12} heterocyclicalkyl, C_1 to C_{12} substituted heterocyclicalkyl, heteroaryl, substituted heteroaryl, heterocycle and substituted heterocycle;

R_3 is a hydrogen atom, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, phenyl, substituted phenyl, heteroaryl, substituted heteroaryl, carboxy, protected carboxy, cyano, protected (monosubstituted)amino, (disubstituted)amino, C_1 to C_{12} acyl, C_1 to C_{12} substituted acyl, C_1 to C_{12} alkoxycarbonyl, C_1 to C_{12} substituted alkoxycarbonyl, C_1 to C_{12} alkylaminocarbonyl, C_1 to C_{12}

substituted alkylaminocarbonyl, phenylaminocarbonyl, substituted phenylaminocarbonyl, heterocycle, substituted heterocycle, naphthyl, substituted naphthyl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl or C_5 to C_7 substituted cycloalkenyl;

R_4 is absent or is the formula:

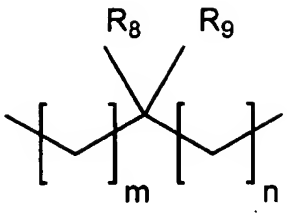
-D-W-E-

wherein:

W is absent or C_3 to C_7 cycloalkylene, C_3 to C_7 substituted cycloalkylene, C_5 to C_7 cycloalkenylene, C_5 to C_7 substituted cycloalkenylene, arylene, substituted arylene, heterocyclene, substituted heterocyclene, heteroarylene or substituted heteroarylene;

and D, which is directly attached to the nitrogen depicted in the formula, and E are independently absent or C_1 to C_{12} alkylene, C_2 to C_{12} alkenylene, C_2 to C_{12} alkynylene, C_1 to C_{12} substituted alkylene, C_2 to C_{12} substituted alkenylene, C_2 to C_{12} substituted alkynylene, C_3 to C_7 cycloalkylene, C_3 to C_7 substituted cycloalkylene, C_5 to C_7 cycloalkenylene, C_5 to C_7 substituted cycloalkenylene, C_7 to C_{18} phenylalkylene, C_7 to C_{18} substituted phenylalkylene, C_1 to C_{12} heterocyclicalkylene, C_1 to C_{12} substituted heterocyclicalkylene;

or the formula:



wherein:

R_8 and R_9 are together or independently a hydrogen atom, C_1 to C_{12} alkyl, C_2 to C_{12} alkenyl, C_2 to C_{12} alkynyl, C_1 to C_{12} substituted alkyl, C_2 to C_{12} substituted alkenyl, C_2 to C_{12} substituted alkynyl, C_1 to C_{12} acyl, C_1 to C_{12} substituted acyl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl, C_5 to C_7 substituted cycloalkenyl, a heterocyclic ring, substituted heterocyclic ring, heteroaryl, substituted heteroaryl, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, C_1 to C_{12} heterocyclicalkyl, C_1 to C_{12} substituted heterocyclicalkyl, C_7 to C_{18} phenylalkoxy, C_7 to C_{18} substituted phenylalkoxy, phenyl, substituted phenyl, naphthyl, substituted naphthyl, cyclic C_2 to C_7 alkylene, substituted cyclic C_2 to C_7 alkylene, cyclic C_2 to C_7 heteroalkylene, substituted cyclic C_2 to C_7 heteroalkylene, carboxy, protected carboxy, hydroxymethyl, protected hydroxymethyl, amino or amino-protecting group; and m and n are independently 0, 1, 2, 3 or 4;

R_5 is absent or -O-, -S-, amino, (monosubstituted)amino, protected (monosubstituted)amino, or one of the following

three formulae: (1) the formula -D-W-E- as defined herein, or (2) the formula K-L-M, wherein K and M are, independently, amino, (monosubstituted)amino or protected (monosubstituted)amino, and L is absent or C_1 to C_{12} alkylene, C_1 to C_{12} substituted alkylene, C_2 to C_{12} alkenylene, C_2 to C_{12} substituted alkenylene, C_3 to C_7 cycloalkylene, C_3 to C_7 substituted cycloalkylene, C_5 to C_7 cycloalkenylene, C_5 to C_7 substituted cycloalkenylene, arylene, substituted arylene, heterocyclene, substituted heterocyclene, heteroarylene or substituted heteroarylene, or (3) the formula $-NR_{12}-$ wherein R_{12} is a hydrogen atom, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, C_1 to C_{12} heterocyclicalkyl, C_1 to C_{12} substituted heterocyclicalkyl, C_7 to C_{18} phenylalkoxy, C_7 to C_{18} substituted phenylalkoxy C_1 to C_{12} acyl, C_1 to C_{12} substituted acyl, phenylsulfonyl, substituted phenylsulfonyl, C_1 to C_{10} alkylsulfonyl, C_1 to C_{10} substituted alkylsulfonyl, C_1 to C_{12} alkylaminocarbonyl, C_1 to C_{12} substituted alkylaminocarbonyl, phenylaminocarbonyl, substituted phenylaminocarbonyl, C_1 to C_{12} alkylaminothiocarbonyl, C_1 to C_{12} substituted alkylaminothiocarbonyl, phenylaminothiocarbonyl, substituted phenylaminothiocarbonyl, amino, (monosubstituted)amino, (disubstituted)amino, protected (monosubstituted)amino, C_1 to C_{12} alkylamino, C_1 to C_{12} alkyl(monosubstituted)amino, C_1 to C_{12} alkyl(disubstituted)amino, C_1 to C_{12} alkyl protected (monosubstituted)amino, C_1 to C_{12} substituted alkylamino, C_1 to C_{12} substituted alkyl(monosubstituted)amino, C_1 to C_{12} substituted alkyl(disubstituted)amino or C_1 to C_{12} substituted alkyl protected (monosubstituted)amino;

R_6 is absent or C_1 to C_{12} alkylene, C_1 to C_{12} substituted alkylene, C_2 to C_{12} alkenylene and C_2 to C_{12} substituted alkenylene; and

R_7 is a hydrogen atom, a halide, $-OR_{13}$, $-CO_2R_{13}$, $-C(O)NR_{13}R_{14}$ and $-NR_{13}R_{14}$, wherein R_{13} and R_{14} are independently a functionalized resin, a hydrogen atom, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, phenyl, substituted phenyl, heterocycle, substituted heterocycle, heteroaryl, substituted heteroaryl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl, C_5 to C_7 substituted cycloalkenyl, C_7 to C_{18} phenylalkyl, C_7 to C_{12} substituted phenylalkyl, C_1 to C_{12} heterocyclicalkyl, C_1 to C_{12} substituted heterocyclicalkyl, C_1 to C_{12} acyl, C_1 to C_{12} substituted acyl, phenylsulfonyl, substituted phenylsulfonyl, C_1 to C_{10} alkylsulfonyl, C_1 to C_{10} substituted alkylsulfonyl, C_1 to C_{12} alkylaminocarbonyl, C_1 to C_{12} substituted alkylaminocarbonyl, phenylaminocarbonyl, substituted phenylaminocarbonyl, C_1 to C_{12} alkylaminothiocarbonyl, C_1 to C_{12} substituted alkylaminothiocarbonyl, phenylaminothiocarbonyl or substituted phenylaminothiocarbonyl;

X, Y and Z are, independently, a hydrogen atom, halo, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_{12} alkyl, C_2 to C_{12} alkenyl, C_2 to C_{12} alkynyl, C_1 to C_{12} substituted alkyl, C_2 to C_{12} substituted alkenyl, C_2 to C_{12} substituted alkynyl, C_1 to C_{12} alkoxy, C_1 to C_{12} substituted alkoxy, C_1 to C_{12} acyloxy, C_1 to C_{12} acyl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl, C_5 to C_7 substituted cycloalkenyl, heterocyclic ring, substituted heterocyclic ring, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, C_1 to C_{12} heterocyclicalkyl, C_1 to C_{12} substituted heterocyclicalkyl, phenyl, substituted

phenyl, naphthyl, substituted naphthyl, cyclic C_2 to C_7 alkylene, substituted cyclic C_2 to C_7 alkylene, cyclic C_2 to C_7 heteroalkylene, substituted cyclic C_2 to C_7 heteroalkylene, carboxy, protected carboxy, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, C_1 to C_{10} alkylthio, C_1 to C_{10} substituted alkylthio, C_1 to C_{10} alkylsulfonyl, C_1 to C_{10} substituted alkylsulfonyl, C_1 to C_{10} alkylsulfoxide, C_1 to C_{10} substituted alkylsulfoxide, phenylthio, substituted phenylthio, phenylsulfoxide, substituted phenylsulfoxide, phenylsulfonyl or substituted phenylsulfonyl; and

b, c and d are, independently, 0 or 1 and, when 0, the absent carbonyl can be replaced with $-SO_2-$.

The invention also provides for pharmaceutically acceptable salts of the above-described compounds.

In a preferred embodiment of the above-described compounds and libraries, R_3 is present, i.e., is not a hydrogen atom.

In another preferred embodiment of the above-described compounds and libraries, R_1 is a hydrogen atom, b is 1, d is 0 and R_2 is C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, C_2 to C_{12} alkenyl, C_2 to C_{12} substituted alkenyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, C_1 to C_{12} heterocyclicalkyl, C_1 to C_{12} substituted heterocyclicalkyl, heteroaryl, substituted heteroaryl, heterocycle or substituted heterocycle.

In an additional preferred embodiment of the above-described compounds and libraries, R_3 is phenyl, substituted phenyl, heteroaryl, substituted heteroaryl, heterocycle, substituted heterocycle, naphthyl and substituted naphthyl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl or C_5 to C_7 substituted cycloalkenyl.

An additional preferred embodiment of the above-described compounds and libraries provides R_4 as the formula:

-D-W-E-

wherein:

W is absent or arylene or substituted arylene; and

D and E are independently absent or independently C_1 to C_{12} alkylene or C_1 to C_{12} substituted alkylene.

In a further preferred embodiment of the above-described compounds and libraries, c is 1.

A further preferred embodiment of the above-described compounds and libraries provides R_5 as absent or -O-; the formula -D-W-E- wherein W is heterocyclene or substituted heterocyclene and D and E are independently absent or independently C_1 to C_{12} alkylene or C_1 to C_{12} substituted alkylene; or the formula $-NR_{12}-$, wherein R_{12} is a hydrogen atom, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, C_1 to C_{12} heterocyclicalkyl, C_1 to C_{12} substituted heterocyclicalkyl, C_7 to C_{18} phenylalkoxy,

C_7 to C_{18} substituted phenylalkoxy, C_1 to C_{12} acyl, C_1 to C_{12} substituted acyl, phenylsulfonyl, substituted phenylsulfonyl, C_1 to C_{10} alkylsulfonyl, C_1 to C_{10} substituted alkylsulfonyl, C_1 to C_{12} alkylaminocarbonyl, C_1 to C_{12} substituted alkylaminocarbonyl, phenylaminocarbonyl, substituted phenylaminocarbonyl, C_1 to C_{12} alkylaminothiocarbonyl, C_1 to C_{12} substituted alkylaminothiocarbonyl, phenylaminothiocarbonyl, substituted phenylaminothiocarbonyl, amino, (monosubstituted)amino, (disubstituted)amino, protected (monosubstituted)amino, C_1 to C_{12} alkylamino, C_1 to C_{12} alkyl(monosubstituted)amino, C_1 to C_{12} alkyl(disubstituted)amino, C_1 to C_{12} alkyl protected (monosubstituted)amino, C_1 to C_{12} substituted alkylamino, C_1 to C_{12} substituted alkyl(monosubstituted)amino, C_1 to C_{12} substituted alkyl(disubstituted)amino or C_1 to C_{12} substituted alkyl protected (monosubstituted)amino.

In another preferred embodiment of the above-described compounds and libraries, R_6 is C_1 to C_{12} alkylene.

Another preferred embodiment of the above-described compounds and libraries provides R_7 as $-C(O)NR_{13}R_{14}$, wherein R_{13} and R_{14} are independently a functionalized resin, a hydrogen atom, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, phenyl, substituted phenyl, heterocycle, substituted heterocycle, heteroaryl, substituted heteroaryl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl, C_5 to C_7 substituted cycloalkenyl, C_7 to C_{18} phenylalkyl, C_7 to C_{12} substituted phenylalkyl, C_1 to C_{12} heterocyclicalkyl, C_1 to C_{12} substituted heterocyclicalkyl, C_1 to C_{12} acyl, C_1 to C_{12} substituted acyl, phenylsulfonyl, substituted

phenylsulfonyl, C_1 to C_{10} alkylsulfonyl, C_1 to C_{10} substituted alkylsulfonyl, C_1 to C_{12} alkylaminocarbonyl, C_1 to C_{12} substituted alkylaminocarbonyl, phenylaminocarbonyl, substituted phenylaminocarbonyl, C_1 to C_{12} alkylaminothiocarbonyl, C_1 to C_{12} substituted alkylaminothiocarbonyl, phenylaminothiocarbonyl or substituted phenylaminothiocarbonyl.

In another preferred embodiment of the above-described compounds and libraries, X, Y and Z are each a hydrogen atom.

In an additional preferred embodiment of the above-described compounds and libraries,

R_1 is a hydrogen atom, b is 1, d is 0 and R_2 is 4-(trifluoromethoxy)phenyl, 2,6-difluorophenyl, 2-pyrazinyl, 2-furyl, 2,3,5,6-tetrafluoro-p-toluenyl, 3,4-difluorophenyl, (4-formylphenoxy)methyl, 2-(2-(trifluoromethyl))vinyl, (diethylphosphonyl)methyl, 2-fluoro-3-(trifluoromethyl)phenyl, 2-fluorophenyl, 4-cyanophenyl, (4-acetylphenoxy)methyl, 1-(phenyl)cyclopropyl, (3-phthalyl)methyl, mesitylformyl, 2-(6-methylchromyl), (2-naphthoxy)methyl, 3,5-bis(trifluoromethyl)phenyl, 3-(2-chloropyridyl), 2-(ethoxycarbonyl)vinyl, 5-(2-methylpyrazyl), 2-bromo-5-methoxyphenyl, 4-iodophenyl, 2-bromophenyl, 5-(4-methyl-1,2,3-thiadiazolyl), 2-(3,4,5-trimethoxyphenyl)vinyl, 2-(methylthio)phenyl, 3-(trifluoromethyl)benzyl, 2-methylcyclopropyl, 2-pentyl, methoxymethyl, 4-heptyl, 3,5,5-trimethylpentyl, allyl, 2-cyclopentylethyl, pentyl, 2-(tetrahydrofuryl), octyl, 2-cyclohexylethyl, heptyl, 3-methoxycyclohexyl, 4-methylcyclohexyl, 2-methylthioethyl, 2-methoxyethyl,

(cyclopentyl)methyl, 2-methylnorbornyl or (methylthio)methyl;

R_3 is phenyl, 1-naphthyl, 3-cyanophenyl, 2-imidazolyl, 2-pyridyl, 3-pyridyl, 2-quinolyl, 4-methylphenyl, 4-(3-dimethylaminopropoxy)phenyl, 4-(methylthio)phenyl, 4-(trifluoromethyl)phenyl, 3,5-dimethoxyphenyl, 3,4-difluorophenyl, 4-tert-butylphenyl, 4-acetamidophenyl, 3-(3,4-dichlorophenoxy)phenyl, 2-fluoryl, 2-(4-dimethylaminophenyl)vinyl, 4-dimethylaminophenyl or 2-propyl;

R_4 is 1,2-ethylene;

c is 1;

R_5 is $-NR_{12}-$, wherein R_{12} is 2-(piperidyl)ethyl, 3-(imidazoyl)propyl, 2,4-dichlorophenethyl, 2-(2-pyridyl)ethyl, (3-pyridyl)methyl, 3-(trifluoromethyl)phenyl, 3-ethoxypropyl, 2-(4-morpholyl)ethyl, N-acetylamino, allyl, phenylmethyl, cyclopropyl, carbomethyoxyamino, 2(N,N-dibutylamino)ethyl, 2(N,N-dimethylamino)ethyl, propyl, 2-(4-methoxyphenyl)ethyl, cyclohexylmethyl, 3-diethylaminopropyl, 4-methylpiprazyl, 3-methoxybenzyl, (2-(1-ethyl-pyrrolidyl))methyl or 2-methoxyethyl;

R_6 is methylene;

R_7 is $-C(O)NH_2$; and

X, Y and Z are each a hydrogen atom.

In an additional preferred embodiment of the above-described compounds and libraries,

R_1 is a hydrogen atom, b is 1, d is 0 and R_2 is 4-(trifluoromethoxy)phenyl, 2,6-difluorophenyl, 2-pyrazinyl, 2-furyl, 2,3,5,6-tetrafluoro-p-toluenyl, 3,4-difluorophenyl, (4-formylphenoxy)methyl, 2-(2-(trifluoromethyl))vinyl, (diethylphosphonyl)methyl, 2-fluoro-3-(trifluoromethyl)phenyl, 2-fluorophenyl, 4-cyanophenyl, (4-acetylphenoxy)methyl, 1-(phenyl)cyclopropyl, (3-phthalyl)methyl, mesitylformyl, 2-(6-methylchromyl), (2-naphthoxy)methyl, 3,5-bis(trifluoromethyl)phenyl, 3-(2-chloropyridyl), 2-(ehtoxycarbonyl)vinyl, 5-(2-methylpyrazyl), 2-bromo-5-methoxyphenyl, 4-iodophenyl, 2-bromophenyl, 5-(4-methyl-1,2,3-thiadiazolyl), 2-(3,4,5-trimethoxyphenyl)vinyl, 2-(methylthio)phenyl, 3-(trifluoromethyl)benzyl, 2-methylcyclopropyl, 2-pentyl, methoxymethyl, 4-heptyl, 3,5,5-trimethylpentyl, allyl, 2-cyclopentylethyl, pentyl, 2-(tetrahydrofuryl), octyl, 2-cyclohexylethyl, heptyl, 3-methoxycyclohexyl, 4-methylcyclohexyl, 2-methylthioethyl, 2-methoxyethyl, (cyclopentyl)methyl, 2-methylnorbornyl or (methylthio)methyl;

R_3 is phenyl, 1-naphthyl, 3-cyanophenyl, 2-imidazolyl, 2-pyridyl, 3-pyridyl, 2-quinolyl, 4-methylphenyl, 4-(3-dimethylaminopropoxy)phenyl, 4-(methylthio)phenyl, 4-(trifluoromethyl)phenyl, 3,5-dimethoxyphenyl, 3,4-difluorophenyl, 4-tert-butylphenyl, 4-acetamidophenyl, 3-(3,4-dichlorophenoxy)phenyl, 2-fluoryl, 2-(4-dimethylaminophenyl)vinyl, 4-dimethylaminophenyl or 2-propyl;

R_4 is the formula -D-W-E-, wherein D is methylene, W is phenylene and E is absent;

c is 1;

R_5 is $-NR_{12}-$, wherein R_{12} is 2-(piperidyl)ethyl, 3-(imidazoyl)propyl, 2,4-dichlorophenethyl, 2-(2-pyridyl)ethyl, (3-pyridyl)methyl, 3-(trifluoromethyl)phenyl, 3-ethoxypropyl, 2-(4-morpholyl)ethyl, N-acetylamino, allyl, phenylmethyl, cyclopropyl, carbomethyoxyamino, 2(N,N-dibutylamino)ethyl, 2(N,N-dimethylamino)ethyl, propyl, 2-(4-methoxyphenyl)ethyl, cyclohexylmethyl, 3-diethylaminopropyl, 4-methylpiprazyl, 3-methoxybenzyl, (2-(1-ethyl-pyrrolidyl))methyl or 2-methoxyethyl;

R_6 is methylene;

R_7 is $-C(O)NH_2$; and

X, Y and Z are each a hydrogen atom.

In a further preferred embodiment of the above-described compounds and libraries,

R_1 is a hydrogen atom, b is 1, d is 0 and R_2 is 4-(trifluoromethoxy)phenyl, 2,6-difluorophenyl, 2-pyrazinyl, 2-furyl, 2,3,5,6-tetrafluoro-p-toluenyl, 3,4-difluorophenyl, (4-formylphenoxy)methyl, 2-(2-(trifluoromethyl))vinyl, (diethylphosphonyl)methyl, 2-fluoro-3-(trifluoromethyl)phenyl, 2-fluorophenyl, 4-cyanophenyl, (4-acetylphenoxy)methyl, 1-(phenyl)cyclopropyl, (3-phthalyl)methyl, mesitylformyl, 2-(6-methylchromyl), (2-naphthoxy)methyl,

3,5-bis(trifluoromethyl)phenyl, 3-(2-chloropyridyl), 2-(ehtoxycarbonyl)vinyl, 5-(2-methylpyrazyl), 2-bromo-5-methoxyphenyl, 4-iodophenyl, 2-bromophenyl, 5-(4-methyl-1,2,3-thiadiazolyl), 2-(3,4,5-trimethoxyphenyl)vinyl, 2-(methylthio)phenyl, 3-(trifluoromethyl)benzyl, 2-methylcyclopropyl, 2-pentyl, methoxymethyl, 4-heptyl, 3,5,5-trimethylpentyl, allyl, 2-cyclopentylethyl, pentyl, 2-(tetrahydrofuryl), octyl, 2-cyclohexylethyl, heptyl, 3-methoxycyclohexyl, 4-methylcyclohexyl, 2-methylthioethyl, 2-methoxyethyl, (cyclopentyl)methyl, 2-methylnorbornyl or (methylthio)methyl;

R_3 is phenyl, 1-naphthyl, 3-cyanophenyl, 2-imidazolyl, 2-pyridyl, 3-pyridyl, 2-quinolyl, 4-methylphenyl, 4-(3-dimethylaminopropoxy)phenyl, 4-(methylthio)phenyl, 4-(trifluoromethyl)phenyl, 3,5-dimethoxyphenyl, 3,4-difluorophenyl, 4-tert-butylphenyl, 4-acetamidophenyl, 3-(3,4-dichlorophenoxy)phenyl, 2-fluoryl, 2-(4-dimethylaminophenyl)vinyl, 4-dimethylaminophenyl or 2-propyl;

R_4 is 1,2-ethylene or the formula -D-W-E-, wherein D is methylene, W is phenylene and E is absent;

c is 1;

R_5 is -O- or 1,4-piperazylene;

R_6 is methylene;

R_7 is $-C(O)NH_2$; and

X, Y and Z are each a hydrogen atom.

The invention also provides methods for making DHQ derivative compounds and libraries. In one method of the invention, DHQ derivative compounds can be prepared by: (a) coupling a first compound having a leaving group with a second compound of one of the following three formulae: (I) HOOC-variable group-NH-amino protecting group (see Figues 1 to 4), (ii) nucleophilic group-variable group-NH-amino protecting group and (iii) nucleophilic group-sulfonyl-variable group-NH-amino protecting group; (b) reacting the compound resulting from step (a) with an aldehyde compound having a variable group (see Figures 1 to 4); and (c) reacting the compound resulting from step (b) with 4-nitrohomophthalic anhydride (see Figures 1 to 4), optionally substituted at one or more position of the phenyl ring other than the 4-nitro position, resulting in a DHQ derivative compound.

Another method further includes attaching the first compound to solid support.

In an additional method, the leaving group of the first compound is a halide.

In a further method, the first compound is reacted with a protected amine compound having a variable group.

In an additional method, the nitro group of the DHQ derivative compound is reduced.

In another method, the amine resulting from reduction of the nitro group on the DHQ derivative is reacted with a carboxylic acid having a variable group, a halide having a variable group or a sulfonyl halide having a variable group.

When the above-described compounds include one or more chiral centers, the stereochemistry of such chiral centers can independently be in the R or S configuration, or a mixture of the two. The chiral centers can be further designated as R or S or R,S or d,D, l,L or d,l, D,L.

Regarding the compounds and combinatorial libraries described herein, the suffix "ene" added to any of the described terms means that two parts of the substituent are each connected to two other parts in the compound (unless the substituent contains only one carbon, in which case such carbon is connected to two other parts in the compound, for example, methylene).

The term "C_1 to C_{12} alkyl" denotes such radicals as methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, amyl, tert-amyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl and the like. Preferred "C_1 to C_{12} alkyl" groups are methyl, ethyl, iso-butyl, sec-butyl and iso-propyl. Similarly, the term "C_1 to C_{12} alkylene" denotes radicals of 1 to 12 carbons connected to two other parts in the compound.

The term "C_2 to C_{12} alkenyl" denotes such radicals as vinyl, allyl, 2-butenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, 5-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 5-heptenyl, 6-heptenyl, (as well as octenyl, nonenyl, decenyl, undecenyl, dodecenyl radicals attached at any appropriate carbon position and the like) as well as dienes and trienes of straight and branched chains.

The term "C_2 to C_{12} alkynyl" denotes such radicals as ethynyl, propynyl, 2-butynyl, 2-pentynyl, 3-pentynyl, 2- hexynyl, 3-hexynyl, 4-hexynyl, 2-heptynyl, 3-heptynyl, 4- heptynyl, 5-heptynyl (as well as octynyl, nonynyl, decynyl, undecynyl, dodecynyl radicals attached at any appropriate carbon position and the like) as well as di- and tri-ynes of straight and branched chains.

The terms "C_1 to C_{12} substituted alkyl," "C_2 to C_{12} substituted alkenyl," "C_2 to C_{12} substituted alkynyl," "C_1 to C_{12} substituted alkylene," "C_2 to C_{12} substituted alkenylene" and "C_2 to C_{12} substituted alkynylene" denote groups are substituted by one or more, and preferably one or two, halogen, hydroxy, protected hydroxy, oxo, protected oxo, C_3 to C_7 cycloalkyl, phenyl, naphthyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, guanidino, protected guanidino, heterocyclic ring, substituted heterocyclic ring, imidazolyl, indolyl, pyrrolidinyl, C_1 to C_{12} alkoxy, C_1 to C_{12} acyl, C_1 to C_{12} acyloxy, nitro, carboxy, protected carboxy, carbamoyl, carboxamide, protected carboxamide, N-(C_1 to C_{12} alkyl)carboxamide, protected N-(C_1 to C_{12} alkyl)carboxamide, N,N-di(C_1 to C_{12} alkyl)carboxamide, cyano, methylsulfonylamino, thiol, C_1 to C_{10} alkylthio or C_1 to C_{10} alkylsulfonyl groups. The substituted alkyl groups may be substituted once or more, and preferably once or twice, with the same or with different substituents.

Examples of the above substituted alkyl groups include the 2-oxo-prop-1-yl, 3-oxo-but-1-yl, cyanomethyl, nitromethyl, chloromethyl, hydroxymethyl, tetrahydropyranyloxymethyl, trityloxymethyl, propionyloxymethyl, aminomethyl, carboxymethyl,

allyloxycarbonylmethyl, allyloxycarbonylaminomethyl, methoxymethyl, ethoxymethyl, t-butoxymethyl, acetoxymethyl, chloromethyl, bromomethyl, iodomethyl, trifluoromethyl, 6-hydroxyhexyl, 2,4-dichloro(n-butyl), 2-aminopropyl, 1-chloroethyl, 2-chloroethyl, 1-bromoethyl, 2-chloroethyl, 1-fluoroethyl, 2-fluoroethyl, 1- iodoethyl, 2-iodoethyl, 1-chloropropyl, 2-chloropropyl, 3- chloropropyl, 1-bromopropyl, 2-bromopropyl, 3-bromopropyl, 1-fluoropropyl, 2-fluoropropyl, 3-fluoropropyl, 1- iodopropyl, 2-iodopropyl, 3-iodopropyl, 2-aminoethyl, 1- aminoethyl, N-benzoyl-2-aminoethyl, N-acetyl-2-aminoethyl, N-benzoyl-1-aminoethyl, N-acetyl-1-aminoethyl and the like.

Examples of the above substituted alkenyl groups include styrenyl, 3-chloro-propen-1-yl, 3-chloro-buten-1-yl, 3-methoxy-propen-2-yl, 3-phenyl-buten-2-yl, 1-cyano-buten-3-yl and the like. The geometrical isomerism is not critical, and all geometrical isomers for a given substituted alkenyl can be used.

Examples of the above substituted alkynyl groups include phenylacetylen-1-yl, 1-phenyl-2-propyn-1-yl and the like.

The term "oxo" denotes a carbon atom bonded to two additional carbon atoms substituted with an oxygen atom doubly bonded to the carbon atom, thereby forming a ketone moiety.

The term "protected oxo" denotes a carbon atom bonded to two additional carbon atoms substituted with two alkoxy groups or twice bonded to a substituted diol

moiety, thereby forming an acyclic or cyclic ketal moiety.

The term "C_1 to C_{12} alkoxy" as used herein denotes groups such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, t-butoxy and like groups. A preferred alkoxy is methoxy. The term "C_1 to C_{12} substituted alkoxy" means the alkyl portion of the alkoxy can be substituted in the same manner as in relation to C_1 to C_{12} substituted alkyl. Similarly, the term "C_1 to C_{12} phenylalkoxy" as used herein means "C_1 to C_{12} alkoxy" bonded to a phenyl radical.

The term "C_1 to C_{12} acyloxy" denotes herein groups such as formyloxy, acetoxy, propionyloxy, butyryloxy, pivaloyloxy, pentanoyloxy, hexanoyloxy, heptanoyloxy, octanoyloxy, nonanoyloxy, decanoyloxy, undecanoyloxy, dodecanoyloxy and the like.

Similarly, the term "C_1 to C_{12} acyl" encompasses groups such as formyl, acetyl, propionyl, butyryl, pentanoyl, pivaloyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, dodecanoyl, benzoyl and the like. Preferred acyl groups are acetyl and benzoyl.

The term "C_1 to C_{12} substituted acyl" denotes the acyl group substituted by one or more, and preferably one or two, halogen, hydroxy, protected hydroxy, oxo, protected oxo, cyclohexyl, naphthyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, guanidino, heterocyclic ring, substituted heterocyclic ring, imidazolyl, indolyl, pyrrolidinyl, C_1 to C_{12} alkoxy, C_1 to C_{12} acyl, C_1 to C_{12} acyloxy, nitro, C_1 to C_{12} alkyl ester,

carboxy, protected carboxy, carbamoyl, carboxamide, protected carboxamide, N-(C_1 to C_{12} alkyl)carboxamide, protected N-(C_1 to C_{12} alkyl)carboxamide, N,N-di(C_1 to C_{12} alkyl)carboxamide, cyano, methylsulfonylamino, thiol, C_1 to C_{10} alkylthio or C_1 to C_{10} alkylsulfonyl groups. The substituted acyl groups may be substituted once or more, and preferably once or twice, with the same or with different substituents.

Examples of C_1 to C_{12} substituted acyl groups include 4-phenylbutyroyl, 3-phenylbutyroyl, 3-phenylpropanoyl, 2- cyclohexanylacetyl, cyclohexanecarbonyl, 2-furanoyl and 3-dimethylaminobenzoyl.

The substituent term "C_3 to C_7 cycloalkyl" includes the cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl rings. Similarly, a substituent that can be C_3 to C_7 cycloalkyl" can also be "C_5 to C_7 cycloalkyl," which includes the cyclopentyl, cyclohexyl or cycloheptyl rings.

The substituent term "C_3 to C_7 substituted cycloalkyl" or "C_5 to C_7 substituted cycloalkyl" indicates the above cycloalkyl rings substituted by one or two halogen, hydroxy, protected hydroxy, C_1 to C_{10} alkylthio, C_1 to C_{10} alkylsulfoxide, C_1 to C_{10} alkylsulfonyl, C_1 to C_{10} substituted alkylthio, C_1 to C_{10} substituted alkylsulfoxide, C_1 to C_{10} substituted alkylsulfonyl, C_1 to C_{12} alkyl, C_1 to C_{12} alkoxy, C_1 to C_{12} substituted alkyl, C_1 to C_{12} alkoxy, oxo, protected oxo, (monosubstituted)amino, (disubstituted)amino, trifluoromethyl, carboxy, protected carboxy, phenyl, substituted phenyl, phenylthio,

phenylsulfoxide, phenylsulfonyl, amino, or protected amino groups.

The term "cycloalkylene" means a cycloalkyl, as defined above, where the cycloalkyl radical is bonded at two positions connecting together two separate additional groups. Similarly, the term "substituted cycloalkylene" means a cycloalkylene where the cycloalkyl radical is bonded at two positions connecting together two separate additional groups and further bearing at least one additional substituent.

The term "C_5 to C_7 cycloalkenyl" indicates a 1,2, or 3-cyclopentenyl ring, a 1,2,3 or 4-cyclohexenyl ring or a 1,2,3,4 or 5-cycloheptenyl ring, while the term "substituted C_5 to C_7 cycloalkenyl" denotes the above C_5 to C_7 cycloalkenyl rings substituted by a C_1 to C_{12} alkyl radical, halogen, hydroxy, protected hydroxy, C_1 to C_{12} alkoxy, trifluoromethyl, carboxy, protected carboxy, oxo, protected oxo, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, phenyl, substituted phenyl, amino, or protected amino.

The term "C_5 to C_7 cycloalkenylene" is a cycloalkenyl ring, as defined above, where the cycloalkenyl radical is bonded at two positions connecting together two separate additional groups. Similarly, the term "substituted C_5 to C_7 cycloalkenylene" means a cycloalkenylene further substituted by halogen, hydroxy, protected hydroxy, C_1 to C_{10} alkylthio, C_1 to C_{10} alkylsulfoxide, C_1 to C_{10} alkylsulfonyl, C_1 to C_{10} substituted alkylthio, C_1 to C_{10} substituted alkylsulfoxide, C_1 to C_{10} substituted alkylsulfonyl, C_1 to C_{12} alkyl, C_1 to C_{12} alkoxy, C_1 to C_{12} substituted alkyl, C_1

to C_{12} alkoxy, oxo, protected oxo, (monosubstituted)amino, (disubstituted)amino, trifluoromethyl, carboxy, protected carboxy, phenyl, substituted phenyl, phenylthio, phenylsulfoxide, phenylsulfonyl, amino, or protected amino group.

The term "heterocycle" or "heterocyclic ring" denotes optionally substituted five-membered or six-membered rings that have 1 to 4 heteroatoms, such as oxygen, sulfur and/or nitrogen, in particular nitrogen, either alone or in conjunction with sulfur or oxygen ring atoms. These five-membered or six-membered rings may be saturated, fully unsaturated or partially unsaturated, with fully saturated rings being preferred. Preferred heterocyclic rings include morpholino, piperidinyl, piperazinyl, 2-amino-imidazoyl, tetrahydrofurano, pyrrolo, and tetrahydrothiophen-yl.

The term "substituted heterocycle" or "substituted heterocyclic ring" means the above-described heterocyclic ring is substituted with, for example, one or more, and preferably one or two, substituents which are the same or different which substituents can be halogen, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_{12} alkyl, C_1 to C_{12} alkoxy, C_1 to C_{12} substituted alkoxy, C_1 to C_{12} acyl, C_1 to C_{12} acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino carboxamide, protected carboxamide, N-(C_1 to C_{12} alkyl)carboxamide, protected N-(C_1 to C_{12} alkyl)carboxamide, N, N-di(C_1 to C_{12} alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_{12} alkyl)sulfonyl)amino, N-

(phenylsulfonyl)amino, heterocycle or substituted heterocycle groups.

The term "heteroaryl" means a heterocyclic aromatic derivative which is a five-membered or six-membered ring system having from 1 to 4 heteroatoms, such as oxygen, sulfur and/or nitrogen, in particular nitrogen, either alone or in conjunction with sulfur or oxygen ring atoms. Examples of heteroaryls include pyridinyl, pyrimidinyl, and pyrazinyl, pyridazinyl, pyrrolo, furano, oxazolo, isoxazolo, phthalimido, thiazolo and the like.

The term "substituted heteroaryl" means the above-described heteroaryl is substituted with, for example, one or more, and preferably one or two, substituents which are the same or different which substituents can be halogen, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_{12} alkyl, C_1 to C_{12} alkoxy, C_1 to C_{12} substituted alkoxy, C_1 to C_{12} acyl, C_1 to C_{12} substituted acyl, C_1 to C_{12} acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, N-(C_1 to C_{12} alkyl)carboxamide, protected N-(C_1 to C_{12} alkyl)carboxamide, N, N-di(C_1 to C_{12} alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_{12} alkyl)sulfonyl)amino or N-(phenylsulfonyl)amino groups.

The term "C_7 to C_{18} phenylalkyl" denotes a C_1 to C_{12} alkyl group substituted at any position within the alkyl chain by a phenyl. The definition includes groups of the formula: -phenyl-alkyl, -alkyl-phenyl and -alkyl-

phenyl-alkyl. Examples of such a group include benzyl, 2-phenylethyl, 3-phenyl(n-propyl), 4-phenylhexyl, 3-phenyl(n-amyl), 3-phenyl(sec-butyl) and the like. Preferred C_7 to C_{18} phenylalkyl groups are any one of the preferred alkyl groups described herein combined with a phenyl group.

Similarly, the term "C_1 to C_{12} heterocyclicalkyl" denotes a C_1 to C_{12} alkyl group substituted at any position within the alkyl chain by a "heterocycle," as defined herein. The definition includes groups of the formula: -heterocyclic-alkyl, -alkyl-heterocyclic and -alkyl-heterocyclic-alkyl. Examples of such a group include 2-pyridylethyl, 3-pierydyl(n-propyl), 4-furylhexyl, 3-piperazyl(n-amyl), 3-morpholyl(sec-butyl) and the like. Preferred C_1 to C_{12} heterocyclicalkyl groups are any one of the preferred alkyl groups described herein combined with any one of the preferred heterocycle groups described herein.

The terms "C_7 to C_{18} substituted phenylalkyl" and "C_1 to C_{12} substituted heterocyclicalkyl" denote a C_7 to C_{18} phenylalkyl group or C_1 to C_{12} heterocyclicalkyl substituted (on the alkyl or, where applicable, phenyl or heterocyclic portion) with one or more, and preferably one or two, groups chosen from halogen, hydroxy, protected hydroxy, oxo, protected oxo, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, guanidino, protected guanidino, heterocyclic ring, substituted heterocyclic ring, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, C_1 to C_{12} alkoxy, C_1 to C_{12} substituted alkoxy, C_1 to C_{12} acyl, C_1 to C_{12} substituted acyl, C_1 to C_{12} acyloxy, nitro, carboxy, protected carboxy, carbamoyl,

carboxamide, protected carboxamide, N-(C_1 to C_{12} alkyl)carboxamide, protected N-(C_1 to C_{12} alkyl)carboxamide, N, N-(C_1 to C_{12} dialkyl)carboxamide, cyano, N-(C_1 to C_{12} alkylsulfonyl)amino, thiol, C_1 to C_{10} alkylthio, C_1 to C_{10} alkylsulfonyl groups; and/or the phenyl group may be substituted with one or more, and preferably one or two, substituents chosen from halogen, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, C_1 to C_{12} alkoxy, C_1 to C_{12} substituted alkoxy, C_1 to C_{12} acyl, C_1 to C_{12} substituted acyl, C_1 to C_{12} acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, N-(C_1 to C_{12} alkyl)carboxamide, protected N-(C_1 to C_{12} alkyl)carboxamide, N, N-di(C_1 to C_{12} alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_{12} alkyl)sulfonyl)amino, N-(phenylsulfonyl)amino, cyclic C_2 to C_{12} alkylene or a phenyl group, substituted or unsubstituted, for a resulting biphenyl group. The substituted alkyl, phenyl or heterocyclic groups may be substituted with one or more, and preferably one or two, substituents which can be the same or different.

Examples of the term "C_7 to C_{18} substituted phenylalkyl" include groups such as 2-phenyl-1-chloroethyl, 2-(4-methoxyphenyl)ethyl, 4-(2,6-dihydroxy phenyl)n-hexyl, 2-(5-cyano-3-methoxyphenyl)n-pentyl, 3-(2,6-dimethylphenyl)n-propyl, 4-chloro-3-aminobenzyl, 6-(4-methoxyphenyl)-3-carboxy(n-hexyl), 5-(4-aminomethylphenyl)- 3-(aminomethyl)n-pentyl, 5-phenyl-3-oxo-n-pent-1-yl and the like.

The term "C_7 to C_{18} phenylalkylene" specifies a C_7 to C_{18} phenylalkyl, as defined above, where the phenylalkyl radical is bonded at two different positions connecting together two separate additional groups. The definition includes groups of the formula: -phenyl-alkyl- and -alkyl-phenyl-alkyl-. Substitutions on the phenyl ring can be 1,2, 1,3 or 1,4.

Similarly, the term "C_1 to C_{12} heterocyclicalkylene" specifies a C_1 to C_{12} heterocyclicalkyl, as defined above, where the heterocyclicalkyl radical is bonded at two different positions connecting together two separate additional groups. The definition includes groups of the formula: -heterocyclic-alkyl-, -alkyl-heterocyclic and -alkyl-heterocyclic-alkyl-.

The terms "C_7 to C_{18} substituted phenylalkylene" and "C_1 to C_{12} substituted heterocyclicalkylene" means a C_7 to C_{18} phenylalkylene or C_1 to C_{12} heterocyclicalkylene as defined above that is further substituted by halogen, hydroxy, protected hydroxy, C_1 to C_{10} alkylthio, C_1 to C_{10} alkylsulfoxide, C_1 to C_{10} alkylsulfonyl, C_1 to C_{10} substituted alkylthio, C_1 to C_{10} substituted alkylsulfoxide, C_1 to C_{10} substituted alkylsulfonyl, C_1 to C_{12} alkyl, C_1 to C_{12} alkoxy, C_1 to C_{12} substituted alkyl, C_1 to C_{12} alkoxy, oxo, protected oxo, (monosubstituted)amino, (disubstituted)amino, trifluoromethyl, carboxy, protected carboxy, phenyl, substituted phenyl, phenylthio, phenylsulfoxide, phenylsulfonyl, amino, or protected amino group on the phenyl ring or on the alkyl group.

The term "substituted phenyl" specifies a phenyl group substituted with one or more, and preferably

one or two, moieties chosen from the groups consisting of halogen, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, C_1 to C_{12} alkoxy, C_1 to C_{12} substituted alkoxy, C_1 to C_{12} acyl, C_1 to C_{12} substituted acyl, C_1 to C_{12} acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, N-(C_1 to C_{12} alkyl)carboxamide, protected N-(C_1 to C_{12} alkyl)carboxamide, N, N-di(C_1 to C_{12} alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_{12} alkyl)sulfonyl)amino, N-(phenylsulfonyl)amino or phenyl, wherein the phenyl is substituted or unsubstituted, such that, for example, a biphenyl results.

Examples of the term "substituted phenyl" includes a mono- or di(halo)phenyl group such as 2, 3 or 4-chlorophenyl, 2,6-dichlorophenyl, 2,5-dichlorophenyl, 3,4-dichlorophenyl, 2, 3 or 4-bromophenyl, 3,4-dibromophenyl, 3-chloro-4-fluorophenyl, 2, 3 or 4-fluorophenyl and the like; a mono or di(hydroxy)phenyl group such as 2, 3 or 4-hydroxyphenyl, 2,4-dihydroxyphenyl, the protected-hydroxy derivatives thereof and the like; a nitrophenyl group such as 2, 3 or 4-nitrophenyl; a cyanophenyl group, for example, 2, 3 or 4-cyanophenyl; a mono- or di(alkyl)phenyl group such as 2, 3 or 4-methylphenyl, 2,4-dimethylphenyl, 2, 3 or 4-(iso-propyl)phenyl, 2, 3 or 4-ethylphenyl, 2, 3 or 4-(n-propyl)phenyl and the like; a mono or di(alkoxyl)phenyl group, for example, 2,6-dimethoxyphenyl, 2, 3 or 4-methoxyphenyl, 2, 3 or 4-ethoxyphenyl, 2, 3 or 4-(isopropoxy)phenyl, 2, 3 or

4-(t-butoxy)phenyl, 3-ethoxy-4-methoxyphenyl and the like; 2, 3 or 4-trifluoromethylphenyl; a mono- or dicarboxyphenyl or (protected carboxy)phenyl group such as 2, 3 or 4-carboxyphenyl or 2,4-di(protected carboxy)phenyl; a mono-or di(hydroxymethyl)phenyl or (protected hydroxymethyl)phenyl such as 2, 3, or 4-(protected hydroxymethyl)phenyl or 3,4-di(hydroxymethyl)phenyl; a mono- or di(aminomethyl)phenyl or (protected aminomethyl)phenyl such as 2, 3 or 4-(aminomethyl)phenyl or 2,4-(protected aminomethyl)phenyl; or a mono- or di(N-(methylsulfonylamino))phenyl such as 2, 3 or 4-(N-(methylsulfonylamino))phenyl. Also, the term "substituted phenyl" represents disubstituted phenyl groups wherein the substituents are different, for example, 3-methyl-4-hydroxyphenyl, 3-chloro-4-hydroxyphenyl, 2-methoxy-4-bromophenyl, 4-ethyl-2-hydroxyphenyl, 3-hydroxy-4-nitrophenyl, 2-hydroxy 4-chlorophenyl and the like.

The term "phenoxy" denotes a phenyl bonded to an oxygen atom, wherein the binding to the rest of the molecule is through the oxygen atom. The term "substituted phenoxy" specifies a phenoxy group substituted with one or more, and preferably one or two, moieties chosen from the groups consisting of halogen, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_{12} alkyl, C_1 to C_{12} alkoxy, C_1 to C_{12} substituted alkoxy, C_1 to C_{12} acyl, C_1 to C_{12} acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, N-(C_1 to C_{12} alkyl)carboxamide, protected N-(C_1 to C_{12}

alkyl)carboxamide, N, N-di(C_1 to C_{12} alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_{12} alkyl)sulfonyl)amino and N-(phenylsulfonyl)amino.

Examples of substituted phenoxy include 2-methylphenoxy, 2-ethylphenoxy, 2-propylphenoxy, 2-isopropylphenoxy, 2-sec-butylphenoxy, 2-tert-butylphenoxy, 2-allylphenoxy, 2-propenylphenoxy, 2-cyclopentylphenoxy, 2-fluorophenoxy, 2-(trifluoromethyl)phenoxy, 2-chlorophenoxy, 2-bromophenoxy, 2-methoxyphenoxy, 2-ethoxyphenoxy, 2-isopropoxyphenoxy, 3-methylphenoxy, 3-ethylphenoxy, 3-isopropylphenoxy, 3-tert-butylphenoxy, 3-pentadecylphenoxy, 3-(trifluoromethyl)phenoxy, 3-fluorophenoxy, 3-chlorophenoxy, 3-bromophenoxy, 3-iodophenoxy, 3-methoxyphenoxy, 3-(trifluoromethoxy)phenoxy, 4-methylphenoxy, 4-ethylphenoxy, 4-propylphenoxy, 4-isopropylphenoxy, 4-sec-butylphenoxy, 4-tert-butylphenoxy, 4-tert-amylphenoxy, 4-nonylphenoxy, 4-dodecylphenoxy, 4-cyclopenylphenoxy, 4-(trifluoromethyl)phenoxy, 4-fluorophenoxy, 4-chlorophenoxy, 4-bromophenoxy, 4-iodophenoxy, 4-methoxyphenoxy, 4-(trifluoromethoxy)phenoxy, 4-ethoxyphenoxy, 4-propoxyphenoxy, 4-butoxyphenoxy, 4-hexyloxyphenoxy, 4-heptyloxyphenoxy, 2,3-dimethylphenoxy, 5,6,7,8-tetrahydro-1-naphthoxy, 2,3-dichlorophenoxy, 2,3-dihydro-2,2-dimethyl-7-benzofuranoxy, 2,3-dimethoxyphenoxy, 2,6-dimethylphenoxy, 2,6-diisopropylphenoxy, 2,6-di-sec-butylphenoxy, 2-tert-butyl-6-methylphenoxy, 2,6-di-tert-butylphenoxy, 2-allyl-6-methylphenoxy, 2,6-difluorophenoxy, 2,3-difluorophenoxy, 2,6-dichlorophenoxy, 2,6-dibromophenoxy, 2-fluoro-6-methoxyphenoxy,

2,6-dimethoxyphenoxy, 3,5-dimethylphenoxy, 5-isopropyl-3-methylphenoxy, 3,5-di-tert-butylphenoxy, 3,5-bis(trifluoromethyl)phenoxy, 3,5-difluorophenoxy, 3,5-dichlorophenoxy, 3,5-dimethoxyphenoxy, 3-chloro-5-methoxyphenoxy, 3,4-dimethylphenoxy, 5-indanoxy, 5,6,7,8-tetrahydro-2-naphthoxy, 4-chloro-3-methylphenoxy, 2,4-dimethylphenoxy, 2,5-dimethylphenoxy, 2-isopropyl-5-methylphenoxy, 4-isopropyl-3-methylphenoxy, 5-isopropyl-2-methylphenoxy, 2-tert-butyl-5-methylphenoxy, 2-tert-butyl-4-methylphenoxy, 2,4-di-tert-butylphenoxy, 2,4-di-tert-amylphenoxy, 4-fluoro-2-methylphenoxy, 4-fluoro-3-methylphenoxy, 2-chloro-4-methylphenoxy, 2-chloro-5-methylphenoxy, 4-chloro-2-methylphenoxy, 4-chloro-3-ethylphenoxy, 2-bromo-4-methylphenoxy, 4-iodo-2-methylphenoxy, 2-chloro-5-(trifluoromethyl)phenoxy, 2,4-difluorophenoxy, 2,5-difluorophenoxy, 3,4-difluorophenoxy, 4-chloro-2-fluorophenoxy, 3-chloro-4-fluorophenoxy, 4-chloro-3-fluorophenoxy, 2-bromo-4-fluorophenoxy, 4-bromo-2-fluorophenoxy, 2-bromo-5-fluorophenoxy, 2,4-dichlorophenoxy, 3,4-dichlorophenoxy, 2,5-dichlorophenoxy, 2-bromo-4-chlorophenoxy, 2-chloro-4-fluorophenoxy, 4-bromo-2-chlorophenoxy, 2,4-dibromophenoxy, 2-methoxy-4-methylphenoxy, 4-allyl-2-methylphenoxy, trans-2-ethoxy-5-(1-propenyl)phenoxy, 2-methoxy-4-propenylphenoxy, 3,4-dimethoxyphenoxy, 3-ethoxy-4-methoxyphenoxy, 4-allyl-2,6-dimethoxyphenoxy, 3,4-methylenedioxyphenoxy, 2,3,6-trimethylphenoxy, 2,4-dichloro-3-methylphenoxy, 2,3,4-trifluorophenoxy, 2,3,6-trifluorophenoxy, 2,3,5-trifluorophenoxy, 2,3,4-trichlorophenoxy, 2,3,6-trichlorophenoxy, 2,3,5-trimethylphenoxy, 3,4,5-trimethylphenoxy, 4-chloro-3,5-dimethylphenoxy, 4-bromo-3,5-dimethylphenoxy, 2,4,6-trimethylphenoxy, 2,6-bis(hydroxymethyl)-4-

methylphenoxy, 2,6-di-tert-butyl-4-methylphenoxy, 2,6-di-tert-butyl-4-methoxyphenoxy, 2,4,5- trifluorophenoxy, 2-chloro-3,5-difluorophenoxy, 2,4,6-trichlorophenoxy, 3,4,5-trimethoxyphenoxy, 2,3,5-trichlorophenoxy, 4-bromo-2,6-dimethylphenoxy, 4-bromo-6-chloro-2-methylphenoxy, 2,6-dibromo-4-methylphenoxy, 2,6-dichloro-4-fluorophenoxy, 2,6-dibromo-4-fluorophenoxy, 2,4,6-tribromophenoxy, 2,4,6-triiodophenoxy, 2-chloro-4,5-dimethylphenoxy, 4-chloro-2-isopropyl-5-methylphenoxy, 2-bromo-4,5-difluorophenoxy, 2,4,5-trichlorophenoxy, 2,3,5,6-tetrafluorophenoxy and the like.

The term "C_7 to C_{18} substituted phenylalkoxy" denotes a C_7 to C_{18} phenylalkoxy group bonded to the rest of the molecule through the oxygen atom, wherein the phenylalkyl portion is substituted with one or more, and preferably one or two, groups selected from halogen, hydroxy, protected hydroxy, oxo, protected oxo, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, guanidino, heterocyclic ring, substituted heterocyclic ring, C_1 to C_{12} alkoxy, C_1 to C_{12} acyl, C_1 to C_{12} acyloxy, nitro, carboxy, protected carboxy, carbamoyl, carboxamide, protected carboxamide, N-(C_1 to C_{12} alkyl)carboxamide, protected N-(C_1 to C_{12} alkyl)carboxamide, N, N-(C_1 to C_{12} dialkyl)carboxamide, cyano, N-(C_1 to C_{12} alkylsulfonyl)amino, thiol, C_1 to C_{10} alkylthio, C_1 to C_{10} alkylsulfonyl groups; and/or the phenyl group can be substituted with one or more, and preferably one or two, substituents chosen from halogen, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_{12} alkyl, C_1 to C_{12} alkoxy, C_1 to C_{12} acyl, C_1 to C_{12} acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl,

hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, N-(C_1 to C_{12} alkyl) carboxamide, protected N-(C_1 to C_{12} alkyl) carboxamide, N, N-di(C_1 to C_{12} alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_{12} alkyl)sulfonyl)amino, N-(phenylsulfonyl)amino or a phenyl group, substituted or unsubstituted, for a resulting biphenyl group. The substituted alkyl or phenyl groups may be substituted with one or more, and preferably one or two, substituents which can be the same or different.

Examples of the term "C_7 to C_{18} substituted phenylalkoxy" include groups such as 2-(4-hydroxyphenyl)ethoxy, 4-(4-methoxyphenyl)butoxy, (2R)-3-phenyl-2-amino-propoxy, (2S)-3-phenyl-2-amino-propoxy, 2-indanoxy, 6-phenyl-1-hexanoxy, cinnamyloxy, (+/-)-2-phenyl-1-propoxy, 2,2-dimethyl-3-phenyl-1-propoxy and the like.

The term "phthalimide" means a cyclic imide which is made from phthalic acid, also called 1,2-benzenedicarboxylic acid. The term "substituted phthalimide" specifies a phthalimide group substituted with one or more, and preferably one or two, moieties chosen from the groups consisting of halogen, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_{12} alkyl, C_1 to C_{12} alkoxy, C_1 to C_{12} substituted alkoxy, C_1 to C_{12} acyl, C_1 to C_{12} acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide,

N-(C_1 to C_{12} alkyl)carboxamide, protected N-(C_1 to C_{12} alkyl)carboxamide, N, N-di(C_1 to C_{12} alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_{12} alkyl)sulfonyl)amino and N-(phenylsulfonyl)amino.

Examples of substituted phthalimides include 4,5-dichlorophthalimido, 3-fluorophthalimido, 4-methoxyphthalimido, 3-methylphthalimido, 4-carboxyphthalimido and the like.

The term "substituted naphthyl" specifies a naphthyl group substituted with one or more, and preferably one or two, moieties either on the same ring or on different rings chosen from the groups consisting of halogen, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_6 alkyl, C_1 to C_7 alkoxy, C_1 to C_7 acyl, C_1 to C_7 acyloxy, carboxy, protected carboxy, carboxymethyl, protected carboxymethyl, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, N-(C_1 to C_{12} alkyl)carboxamide, protected N-(C_1 to C_{12} alkyl)carboxamide, N, N-di(C_1 to C_{12} alkyl)carboxamide, trifluoromethyl, N-((C_1 to C_{12} alkyl)sulfonyl)amino or N-(phenylsulfonyl)amino.

Examples of the term "substituted naphthyl" includes a mono or di(halo)naphthyl group such as 1, 2, 3, 4, 5, 6, 7 or 8-chloronaphthyl, 2, 6-dichloronaphthyl, 2, 5-dichloronaphthyl, 3, 4-dichloronaphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-bromonaphthyl, 3, 4-dibromonaphthyl, 3-chloro-4-fluoronaphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-fluoronaphthyl and the like; a mono or di(hydroxy)naphthyl group such as 1, 2, 3, 4, 5, 6, 7 or

8-hydroxynaphthyl, 2, 4-dihydroxynaphthyl, the protected-hydroxy derivatives thereof and the like; a nitronaphthyl group such as 3- or 4-nitronaphthyl; a cyanonaphthyl group, for example, 1, 2, 3, 4, 5, 6, 7 or 8-cyanonaphthyl; a mono- or di(alkyl)naphthyl group such as 2, 3, 4, 5, 6, 7 or 8-methylnaphthyl, 1, 2, 4-dimethylnaphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-(isopropyl)naphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-ethylnaphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-(n-propyl)naphthyl and the like; a mono or di(alkoxy)naphthyl group, for example, 2, 6-dimethoxynaphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-methoxynaphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-ethoxynaphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-(isopropoxy)naphthyl, 1, 2, 3, 4, 5, 6, 7 or 8-(t-butoxy)naphthyl, 3-ethoxy-4-methoxynaphthyl and the like; 1, 2, 3, 4, 5, 6, 7 or 8-trifluoromethylnaphthyl; a mono- or dicarboxynaphthyl or (protected carboxy)naphthyl group such as 1, 2, 3, 4, 5, 6, 7 or 8-carboxynaphthyl or 2, 4-di(-protected carboxy)naphthyl; a mono-or di(hydroxymethyl)naphthyl or (protected hydroxymethyl)naphthyl such as 1, 2, 3, 4, 5, 6, 7 or 8-(protected hydroxymethyl)naphthyl or 3, 4-di(hydroxymethyl)naphthyl; a mono- or di(amino)naphthyl or (protected amino)naphthyl such as 1, 2, 3, 4, 5, 6, 7 or 8-(amino)naphthyl or 2, 4-(protected amino)-naphthyl, a mono- or di(aminomethyl)naphthyl or (protected aminomethyl)naphthyl such as 2, 3, or 4-(aminomethyl)naphthyl or 2, 4-(protected aminomethyl)-naphthyl; or a mono- or di-(N-methylsulfonylamino) naphthyl such as 1, 2, 3, 4, 5, 6, 7 or 8-(N-methylsulfonylamino)naphthyl. Also, the term "substituted naphthyl" represents disubstituted naphthyl groups wherein the substituents are different, for

example, 3-methyl-4-hydroxynaphth-1-yl, 3-chloro-4-hydroxynaphth-2-yl, 2-methoxy-4-bromonaphth-1-yl, 4-ethyl-2-hydroxynaphth-1-yl, 3-hydroxy-4-nitronaphth-2-yl, 2-hydroxy-4-chloronaphth-1-yl, 2-methoxy-7-bromonaphth-1-yl, 4-ethyl-5-hydroxynaphth-2-yl, 3-hydroxy-8-nitronaphth-2-yl, 2-hydroxy-5-chloronaphth-1-yl and the like.

The term "naphthylene" means a naphthyl radical bonded at two positions connecting together two separate additional groups. Similarly, the term "substituted napthylene" means a naphthylene group that is further substituted by halogen, hydroxy, protected hydroxy, C_1 to C_{10} alkylthio, C_1 to C_{10} alkylsulfoxide, C_1 to C_{10} alkylsulfonyl, C_1 to C_{10} substituted alkylthio, C_1 to C_{10} substituted alkylsulfoxide, C_1 to C_{10} substituted alkylsulfonyl, C_1 to C_{12} alkyl, C_1 to C_{12} alkoxy, C_1 to C_{12} substituted alkyl, C_1 to C_{12} alkoxy, oxo, protected oxo, (monosubstituted)amino, (disubstituted)amino, trifluoromethyl, carboxy, protected carboxy, phenyl, substituted phenyl, phenylthio, phenylsulfoxide, phenylsulfonyl, amino, or protected amino group.

The terms "halo" and "halogen" refer to the fluoro, chloro, bromo or iodo atoms. There can be one or more halogens, which are the same or different. Preferred halogens are chloro and fluoro.

The term "(monosubstituted)amino" refers to an amino group with one substituent chosen from the group consisting of phenyl, substituted phenyl, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, C_1 to C_{12} acyl, C_1 to C_{12} substituted acyl, C_2 to C_{12} alkenyl, C_2 to C_{12} substituted alkenyl, C_2 to C_{12} alkynyl, C_2 to C_{12} substituted alkynyl,

C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, heterocyclic ring, substituted heterocyclic ring, C_1 to C_{12} heterocyclicalkyl and C_1 to C_{12} substituted heterocyclicalkyl. The (monosubstituted)amino can additionally have an amino-protecting group as encompassed by the term "protected (monosubstituted)amino."

The term "(disubstituted)amino" refers to an amino group with two substituents chosen from the group consisting of phenyl, substituted phenyl, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, C_1 to C_{12} acyl, C_2 to C_{12} alkenyl, C_2 to C_{12} alkynyl, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, C_1 to C_{12} heterocyclicalkyl and C_1 to C_{12} substituted heterocyclicalkyl,. The two substituents can be the same or different.

The term "amino-protecting group" as used herein refers to substituents of the amino group commonly employed to block or protect the amino functionality while reacting other functional groups of the molecule. The term "protected (monosubstituted)amino" means there is an amino-protecting group on the monosubstituted amino nitrogen atom. In addition, the term "protected carboxamide" means there is an amino-protecting group on the carboxamide nitrogen. Similarly, the term "protected N-(C_1 to C_{12} alkyl)carboxamide" means there is an amino-protecting group on the carboxamide nitrogen.

Examples of such amino-protecting groups include the formyl ("For") group, the trityl group, the phthalimido group, the trichloroacetyl group, the chloroacetyl, bromoacetyl, and iodoacetyl groups, urethane-type blocking groups, such as t-butoxycarbonyl

("Boc"), 2-(4-biphenylyl)propyl-2-oxycarbonyl ("Bpoc"), 2-phenylpropyl-2-oxycarbonyl ("Poc"), 2-(4-xenyl)isopropoxycarbonyl, 1,1-diphenylethyl-1-oxycarbonyl, 1,1-diphenylpropyl-1-oxycarbonyl, 2-(3,5-dimethoxyphenyl)propyl-2-oxycarbonyl ("Ddz"), 2-(p-toluyl)propyl-2-oxycarbonyl, cyclopentanyloxycarbonyl, 1-methylcyclopentanyloxycarbonyl, cyclohexanyloxy-carbonyl, 1-methylcyclohexanyloxycarbonyl, 2-methylcyclohexanyloxycarbonyl, 2-(4-toluylsulfonyl)-ethoxycarbonyl, 2-(methylsulfonyl)ethoxycarbonyl, 2-(triphenylphosphino)-ethoxycarbonyl, 9-fluorenylmethoxycarbonyl ("Fmoc"), 2-(trimethylsilyl)ethoxycarbonyl, allyloxycarbonyl, 1-(trimethylsilylmethyl)prop-1-enyloxycarbonyl, 5-benzisoxalylmethoxycarbonyl, 4-acetoxybenzyl-oxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-ethynyl-2-propoxycarbonyl, cyclopropylmethoxycarbonyl, isobornyloxycarbonyl, 1-piperidyloxycarbonyl, benzyloxycarbonyl ("Cbz"), 4-phenylbenzyloxycarbonyl, 2-methylbenzyloxy-carbonyl, -2,4,5,-tetramethylbenzyloxycarbonyl ("Tmz"), 4-methoxybenzyloxycarbonyl, 4-fluorobenzyloxycarbonyl, 4-chlorobenzyloxycarbonyl, 3-chlorobenzyloxycarbonyl, 2-chlorobenzyloxycarbonyl, 2,4-dichlorobenzyl-oxycarbonyl, 4-bromobenzyloxycarbonyl, 3-bromobenzyloxycarbonyl, 4-nitrobenzyloxy-carbonyl, 4-cyanobenzyloxycarbonyl, 4-(decyloxy)benzyloxycarbonyl and the like; the benzoylmethylsulfonyl group, dithiasuccinoyl ("Dts"), the 2-(nitro)phenylsulfenyl group ("Nps"), the diphenyl-phosphine oxide group and like amino-protecting groups. The species of amino-protecting group employed is not critical so long as the derivatized amino group is stable to the conditions of the subsequent reaction(s) and can be removed at the

appropriate point without disrupting the remainder of the compounds. Preferred amino-protecting groups are Boc, Cbz and Fmoc. Further examples of amino-protecting groups embraced by the above term are well known in organic synthesis and the peptide art and are described by, for example, T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis," 2nd ed., John Wiley and Sons, New York, NY, 1991, Chapter 7, M. Bodanzsky, "Principles of Peptide Synthesis," 1st and 2nd revised ed., Springer-Verlag, New York, NY, 1984 and 1993, and Stewart and Young, "Solid Phase Peptide Synthesis," 2nd ed., Pierce Chemical Co., Rockford, IL, 1984, each of which is incorporated herein by reference. The related term "protected amino" defines an amino group substituted with an amino-protecting group discussed above.

The term "protected guanidino" as used herein refers to an "amino-protecting group" on one or two of the guanidino nitrogen atoms. Examples of "protected guanidino" groups are described by T.W. Greene and P.G.M. Wuts; M. Bodanzsky; and Stewart and Young, supra.

The term "carboxy-protecting group" as used herein refers to one of the ester derivatives of the carboxylic acid group commonly employed to block or protect the carboxylic acid group while reactions are carried out on other functional groups on the compound. Examples of such carboxylic acid protecting groups include t-butyl, 4-nitrobenzyl, 4-methoxybenzyl, 3,4-dimethoxybenzyl, 2,4-dimethoxybenzyl, 2,4,6-trimethoxybenzyl, 2,4,6-trimethylbenzyl, pentamethylbenzyl, 3,4-methylenedioxybenzyl, benzhydryl, 4,4'-dimethoxytrityl, 4,4',4"-trimethoxytrityl, 2-phenylpropyl, trimethylsilyl, t-butyldimethylsilyl,

phenacyl, 2,2,2-trichloroethyl, -(trimethylsilyl)ethyl, -(di(n-butyl)methylsilyl)ethyl, p- toluenesulfonylethyl, 4-nitrobenzylsulfonylethyl, allyl, cinnamyl, 1-(trimethylsilylmethyl)-propenyl and like moieties. The species of carboxy-protecting group employed is not critical so long as the derivatized carboxylic acid is stable to the conditions of subsequent reaction(s) and can be removed at the appropriate point without disrupting the remainder of the molecule. Further examples of these groups are found in E. Haslam, "Protective Groups in Organic Chemistry," J.G.W. McOmie, Ed., Plenum Press, New York, NY, 1973, Chapter 5, and T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis," 2nd ed., John Wiley and Sons, New York, NY, 1991, Chapter 5, each of which is incorporated herein by reference. A related term is "protected carboxy," which refers to a carboxy group substituted with one of the above carboxy-protecting groups.

The term "hydroxy-protecting group" refers to readily cleavable groups bonded to hydroxyl groups, such as the tetrahydropyranyl, 2-methoxypropyl, 1-ethoxyethyl, methoxymethyl, 2-methoxyethoxymethyl, methylthiomethyl, t-butyl, t-amyl, trityl, 4-methoxytrityl, 4,4'-dimethoxytrityl, 4,4',4"-trimethoxytrityl, benzyl, allyl, trimethylsilyl, (t-butyl)dimethylsilyl, 2,2,2-trichloroethoxycarbonyl groups and the like. The species of hydroxy-protecting groups is not critical so long as the derivatized hydroxyl group is stable to the conditions of subsequent reaction(s) and can be removed at the appropriate point without disrupting the remainder of the molecule. Further examples of hydroxy-protecting groups are described by C.B. Reese and E. Haslam, "Protective Groups in Organic Chemistry," J.G.W. McOmie,

Ed., Plenum Press, New York, NY, 1973, Chapters 3 and 4, respectively, and T.W. Greene and P.G.M. Wuts, "Protective Groups in Organic Synthesis," 2nd ed., John Wiley and Sons, New York, NY, 1991, Chapters 2 and 3. Related terms are "protected hydroxy," and "protected hydroxymethyl" which refer to a hydroxy or hydroxymethyl substituted with one of the above hydroxy-protecting groups.

The term "C_1 to C_{10} alkylthio" refers to sulfide groups such as methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, t-butylthio and like groups. The term "C_1 to C_{10} alkylsulfoxide" indicates sulfoxide groups such as methylsulfoxide, ethylsulfoxide, n-propylsulfoxide, isopropylsulfoxide, n-butylsulfoxide, sec-butylsulfoxide and the like. The term "C_1 to C_{10} alkylsulfonyl" encompasses groups such as methylsulfonyl, ethylsulfonyl, n-propylsulfonyl, isopropylsulfonyl, n-butylsulfonyl, t-butylsulfonyl and the like. it should also be understood that the above thio, sulfoxide or sulfonyl groups can be at any point on the alkyl chain (e.g., 2-methylmercaptoethyl).

The terms "C_1 to C_{10} substituted alkylthio," "C_1 to C_{10} substituted alkylsulfoxide," and "C_1 to C_{10} substituted alkylsulfonyl," denote the C_1 to C_{10} alkyl portion of these groups may be substituted as described above in relation to "substituted alkyl."

The terms "phenylthio," "phenylsulfoxide," and "phenylsulfonyl" specify a thiol, a sulfoxide, or sulfone, respectively, containing a phenyl group. The terms "substituted phenylthio," "substituted phenylsulfoxide," and "substituted phenylsulfonyl" means

that the phenyl of these groups can be substituted as described above in relation to "substituted phenyl."

The term "C_1 to C_{12} alkylaminocarbonyl" means a C_1 to C_{12} alkyl attached to a nitrogen of the aminocarbonyl group. Examples of C_1 to C_{12} alkylaminocarbonyl include methylaminocarbonyl, ethylaminocarbonyl, propylaminocarbonyl and butylaminocarbonyl. The term "C_1 to C_{12} substituted alkylaminocarbonyl" denotes a substituted alkyl bonded to a nitrogen of the aminocarbonyl group, which alkyl may be substituted as described above in relation to C_1 to C_{12} substituted alkyl. Examples of C_1 to C_{12} substituted alkylaminocarbonyl include, for example, methoxymethylaminocarbonyl, 2-chloroethylaminocarbonyl, 2-oxopropylaminocarbonyl and 4-phenylbutylaminocarbonyl.

The term "C_1 to C_{12} alkoxycarbonyl" means a "C_1 to C_{12} alkoxy" group attached to a carbonyl group. The term "C_1 to C_{12} substituted alkoxycarbonyl" denotes a substituted alkoxy bonded to the carbonyl group, which alkoxy may be substituted as described above in relation to "C_1 to C_{12} substituted alkyl."

The term "phenylaminocarbonyl" means a phenyl attached to a nitrogen of the aminocarbonyl group. The term "substituted phenylaminocarbonyl" denotes a substituted phenyl bonded to a nitrogen of the aminocarbonyl group, which phenyl may be substituted as described above in relation to substituted phenyl. Examples of substituted phenylaminocarbonyl include 2-chlorophenylaminocarbonyl, 3-chlorophenylaminocarbonyl , 2-nitorphenylaminocarbonyl, 4-biphenylaminocarbonyl, and 4-methoxyphenylaminocarbonyl.

The term "C_1 to C_{12} alkylaminothiocarbonyl" means a C_1 to C_{12} alkyl attached to an aminothiocarbonyl group, wherein the alkyl has the same meaning as defined above. Examples of C_1 to C_{12} alkylaminothiocarbonyl include methylaminothiocarbonyl, ethylaminothiocarbonyl, propylaminothiocarbonyl and butylaminothiocarbonyl.

The term "C_1 to C_{12} substituted alkylaminothiocarbonyl" denotes a substituted alkyl bonded to an aminothiocarbonyl group, wherein the alkyl may be substituted as described above in relation to C_1 to C_{12} substituted alkyl. Examples of C_1 to C_{12} substituted alkylaminothiocarbonyl include, for example, methoxymethylaminothiocarbonyl, 2-chloroethylaminothiocarbonyl, 2-oxopropylaminothiocarbonyl and 4-phenylbutylaminothiocarbonyl.

The term "phenylaminothiocarbonyl" means a phenyl attached to an aminothiocarbonyl group, wherein the phenyl has the same meaning as defined above.

The term "substituted phenylaminothiocarbonyl" denotes a substituted phenyl bonded to an aminothiocarbonyl group, wherein phenyl may be substituted as described above in relation to substituted phenyl. Examples of substituted phenylaminothiocarbonyls include 2-chlorophenylaminothiocarbonyl, 3-chlorophenylaminothiocarbonyl, 2nitorphenylaminothiocarbonyl, 4-biphenylaminothiocarbonyl and 4-methoxyphenylaminothiocarbonyl.

The term "phenylene" means a phenyl group where the phenyl radical is bonded at two positions connecting together two separate additional groups. Examples of "phenylene" include 1,2-phenylene, 1,3-phenylene, and 1,4-phenylene.

The term "substituted phenylene" means a phenyl group where the phenyl radical is bonded at two positions connecting together two separate additional groups, wherein the phenyl is substituted as described above in relation to "substituted phenyl."

The term "substituted C_1 to C_{12} alkylene" means a C_1 to C_{12} alkyl group where the alkyl radical is bonded at two positions connecting together two separate additional groups and further bearing an additional substituent. Examples of "substituted C_1 to C_{12} alkylene" includes aminomethylene, 1-(amino)-1,2-ethyl, 2-(amino)-1,2-ethyl, 1-(acetamido)-1,2-ethyl, 2-(acetamido)-1,2-ethyl, 2-hydroxy-1,1-ethyl, 1-(amino)-1,3-propyl.

The terms "cyclic C_2 to C_7 alkylene," "substituted cyclic C_2 to C_7 alkylene," "cyclic C_2 to C_7 heteroalkylene," and "substituted cyclic C_2 to C_7 heteroalkylene," defines such a cyclic group bonded ("fused") to the phenyl radical resulting in a bicyclic ring system. The cyclic group may be saturated or contain one or two double bonds. Furthermore, the cyclic group may have one or two methylene or methine groups replaced by one or two oxygen, nitrogen or sulfur atoms which are the cyclic C_2 to C_7 heteroalkylene.

The cyclic alkylene or heteroalkylene group may be substituted once or twice by the same or different

substituents which, if appropriate, can be connected to another part of the compound (e.g., alkylene) selected from the group consisting of the following moieties: hydroxy, protected hydroxy, carboxy, protected carboxy, oxo, protected oxo, C_1 to C_4 acyloxy, formyl, C_1 to C_{12} acyl, C_1 to C_{12} alkyl, C_1 to C_7 alkoxy, C_1 to C_{10} alkylthio, C_1 to C_{10} alkylsulfoxide, C_1 to C_{10} alkylsulfonyl, halo, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, hydroxymethyl or a protected hydroxymethyl.

The cyclic alkylene or heteroalkylene group fused onto the benzene radical can contain two to ten ring members, but it preferably contains three to six members. Examples of such saturated cyclic groups are when the resultant bicyclic ring system is 2,3-dihydro-indanyl and a tetralin ring. When the cyclic groups are unsaturated, examples occur when the resultant bicyclic ring system is a naphthyl ring or indolyl. Examples of fused cyclic groups which each contain one nitrogen atom and one or more double bond, preferably one or two double bonds, are when the benzene radical is fused to a pyridino, pyrano, pyrrolo, pyridinyl, dihydropyrrolo, or dihydropyridinyl ring. Examples of fused cyclic groups which each contain one oxygen atom and one or two double bonds are when the benzene radical ring is fused to a furo, pyrano, dihydrofurano, or dihydropyrano ring. Examples of fused cyclic groups which each have one sulfur atom and contain one or two double bonds are when the benzene radical is fused to a thieno, thiopyrano, dihydrothieno or dihydrothiopyrano ring. Examples of cyclic groups which contain two heteroatoms selected from sulfur and nitrogen and one or two double bonds are when the benzene radical ring is fused to a thiazolo,

isothiazolo, dihydrothiazolo or dihydroisothiazolo ring. Examples of cyclic groups which contain two heteroatoms selected from oxygen and nitrogen and one or two double bonds are when the benzene ring is fused to an oxazolo, isoxazolo, dihydrooxazolo or dihydroisoxazolo ring. Examples of cyclic groups which contain two nitrogen heteroatoms and one or two double bonds occur when the benzene ring is fused to a pyrazolo, imidazolo, dihydropyrazolo or dihydroimidazolo ring or pyrazinyl.

The term "carbamoyl" means an -NCO- group where the radical is bonded at two positions connecting two separate additional groups.

One or more of the compounds of the invention, even within a given library, may be present as a salt. The term "salt" encompasses those salts that form with the carboxylate anions and amine nitrogens and include salts formed with the organic and inorganic anions and cations discussed below. Furthermore, the term includes salts that form by standard acid-base reactions with basic groups (such as amino groups) and organic or inorganic acids. Such acids include hydrochloric, hydrofluoric, trifluoroacetic, sulfuric, phosphoric, acetic, succinic, citric, lactic, maleic, fumaric, palmitic, cholic, pamoic, mucic, D-glutamic, D-camphoric, glutaric, phthalic, tartaric, lauric, stearic, salicyclic, methanesulfonic, benzenesulfonic, sorbic, picric, benzoic, cinnamic, and like acids.

The term "organic or inorganic cation" refers to counter-ions for the carboxylate anion of a carboxylate salt. The counter-ions are chosen from the alkali and alkaline earth metals, (such as lithium,

sodium, potassium, barium, aluminum and calcium); ammonium and mono-, di- and tri-alkyl amines such as trimethylamine, cyclohexylamine; and the organic cations, such as dibenzylammonium, benzylammonium, 2-hydroxyethylammonium, bis(2-hydroxyethyl)ammonium, phenylethylbenzylammonium, dibenzylethylenediammonium, and like cations. See, for example, "Pharmaceutical Salts," Berge et al., J. Pharm. Sci., 66:1-19 (1977), which is incorporated herein by reference. Other cations encompassed by the above term include the protonated form of procaine, quinine and N-methylglucosamine, and the protonated forms of basic amino acids such as glycine, ornithine, histidine, phenylglycine, lysine and arginine. Furthermore, any zwitterionic form of the instant compounds formed by a carboxylic acid and an amino group is referred to by this term. For example, a cation for a carboxylate anion will exist when a position is substituted with a (quaternary ammonium)methyl group. A preferred cation for the carboxylate anion is the sodium cation.

The compounds of the invention can also exist as solvates and hydrates. Thus, these compounds may crystallize with, for example, waters of hydration, or one, a number of, or any fraction thereof of molecules of the mother liquor solvent. The solvates and hydrates of such compounds are included within the scope of this invention.

One or more compounds of the invention, even when in a library, can be in the biologically active ester form, such as the non-toxic, metabolically-labile ester-form. Such ester forms induce increased blood levels and prolong the efficacy of the corresponding non-

esterified forms of the compounds. Ester groups which can be used include the lower alkoxymethyl groups, for example, methoxymethyl, ethoxymethyl, isopropoxymethyl and the like; the -(C_1 to C_{12}) alkoxyethyl groups, for example methoxyethyl, ethoxyethyl, propoxyethyl, isopropoxyethyl and the like; the 2-oxo-1,3-diooxlen-4-ylmethyl groups, such as 5-methyl-2-oxo-1,3-dioxolen-4-ylmethyl, 5-phenyl-2-oxo-1,3-dioxolen-4-ylmethyl and the like; the C_1 to C_{10} alkylthiomethyl groups, for example methylthiomethyl, ethylthiomethyl, iso-propylthiomethyl and the like; the acyloxymethyl groups, for example pivaloyloxymethyl, pivaloyloxyethyl, -acetoxymethyl and the like; the ethoxycarbonyl-1-methyl group; the -acetoxyethyl; the 1-(C_1 to C_{12} alkyloxycarbonyloxy)ethyl groups such as the 1-(ethoxycarbonyloxy)ethyl group; and the 1-(C_1 to C_{12} alkylaminocarbonyloxy)ethyl groups such as the 1-(methylaminocarbonyloxy)ethyl group.

The term "amino acid" includes any one of the twenty naturally-occurring amino acids or the D-form of any one of the naturally-occurring amino acids. In addition, the term "amino acid" also includes other non-naturally occurring amino acids besides the D-amino acids, which are functional equivalents of the naturally-occurring amino acids. Such non-naturally-occurring amino acids include, for example, norleucine ("Nle"), norvaline ("Nva"), L- or D- naphthalanine, ornithine ("Orn"), homoarginine (homoArg) and others well known in the peptide art, such as those described in M. Bodanzsky, "Principles of Peptide Synthesis," 1st and 2nd revised ed., Springer-Verlag, New York, NY, 1984 and 1993, and Stewart and Young, "Solid Phase Peptide Synthesis," 2nd ed., Pierce Chemical Co., Rockford, IL, 1984, both of which are incorporated herein by reference. Amino acids

and amino acid analogs can be purchased commercially (Sigma Chemical Co.; Advanced Chemtech) or synthesized using methods known in the art.

The term "functionalized resin" means any resin, crosslinked or otherwise, where functional groups have been introduced into the resin, as is common in the art. Such resins include, for example, those functionalized with amino, alkylhalo, formyl or hydroxy groups. Such resins which can serve as solid supports are well known in the art and include, for example, 4-methylbenzhydrylamine-copoly(styrene-1% divinylbenzene) (MBHA), 4-hydroxymethylphenoxymethyl-copoly(styrene-1% divinylbenzene), 4-oxymethyl-phenyl-acetamido-copoly(stryene-1% divinylbenzene)(Wang), 4-(oxymethyl)-phenylacetamido methyl (Pam), and Tentagel™, from Rapp Polymere Gmbh, trialkoxy-diphenyl-methyl ester-copoly(styrene-1% divinylbenzene)(RINK) all of which are commercially available. Other functionalized resins are known in the art and can be use without departure from the scope of the current invention. Such resins may include those described in Jung, G., Combinatorial Peptide and Nonpeptide Libraries, A Handbook (VCH Verlag, 1996) or Bunin, B. A., The Combinatorial Index (Academic Press, 1998) and are incorporated herein by reference.

As used herein, a "combinatorial library" is an intentionally created collection of differing molecules which can be prepared by the means provided below or otherwise and screened for biological activity in a variety of formats (e.g., libraries of soluble molecules, libraries of compounds attached to resin beads, silica chips or other solid supports). A "combinatorial library," as defined above, involves successive rounds of

chemical syntheses based on a common starting structure. The combinatorial libraries can be screened in any variety of assays, such as those detailed below as well as others useful for assessing their biological activity. The combinatorial libraries will generally have at least one active compound and are generally prepared such that the compounds are in equimolar quantities.

Compounds disclosed in previous work that are not disclosed as part of a collection of compounds or not disclosed as intended for use as part of such a collection are not part of a "combinatorial library" of the invention. In addition, compounds that are in an unintentional or undesired mixture are not part of a "combinatorial library" of the invention.

A combinatorial library of the invention can contain two or more of the above-described compounds. The invention further provides a combinatorial library containing three, four or five or more of the above-described compounds. In another embodiment of the invention, a combinatorial library can contain ten or more of the above-described compounds. In yet another embodiment of the invention, a combinatorial library can contain fifty or more of the above-described compounds. If desired, a combinatorial library of the invention can contain 100,000 or more, or even 1,000,000 or more, of the above-described compounds.

By way of example, the preparation of the combinatorial libraries can use the "split resin approach." The split resin approach is described by, for example, U.S. Patent 5,010,175 to Rutter, WO PCT 91/19735 to Simon, and Gallop et al., *J. Med. Chem.*, 37:1233-1251

(1994), all of which are incorporated herein by reference.

The amino acids are indicated herein by either their full name or by the commonly known three letter code. Further, in the naming of amino acids, "D-" designates an amino acid having the "D" configuration, as opposed to the naturally occurring L-amino acids. Where no specific configuration is indicated, one skilled in the art would understand the amino acid to be an L-amino acid. The amino acids can, however, also be in racemic mixtures of the D- and L-configuration or the D-amino acid can readily be substituted for that in the L-configuration.

For preparing pharmaceutical compositions containing compounds of the invention, inert, pharmaceutically acceptable carriers are used. The pharmaceutical carrier can be either solid or liquid. Solid form preparations include, for example, powders, tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances which can also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is generally a finely divided solid which is in a mixture with the finely divided active component. In tablets, the active compound is mixed with the carrier having the necessary

binding properties in suitable proportions and compacted in the shape and size desired.

For preparing pharmaceutical composition in the form of suppositories, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient-sized molds and allowed to cool and solidify.

Powders and tablets preferably contain between about 5% to about 70% by weight of the active ingredient. Suitable carriers include, for example, magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter and the like.

The pharmaceutical compositions can include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier, which is thus in association with it. In a similar manner, cachets are also included. Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

Liquid pharmaceutical compositions include, for example, solutions suitable for oral or parenteral administration, or suspensions, and emulsions suitable for oral administration. Sterile water solutions of the active component or sterile solutions of the active component in solvents comprising water, ethanol, or

propylene glycol are examples of liquid compositions suitable for parenteral administration.

Sterile solutions can be prepared by dissolving the active component in the desired solvent system, and then passing the resulting solution through a membrane filter to sterilize it or, alternatively, by dissolving the sterile compound in a previously sterilized solvent under sterile conditions.

Aqueous solutions for oral administration can be prepared by dissolving the active compound in water and adding suitable flavorants, coloring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural or synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

Preferably, the pharmaceutical composition is in unit dosage form. In such form, the composition is divided into unit doses containing appropriate quantities of the active DHQ compound. The unit dosage form can be a packaged preparation, the package containing discrete quantities of the preparation, for example, packeted tablets, capsules, and powders in vials or ampules. The unit dosage form can also be a capsule, cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms.

As pharmaceutical compositions for treating infections, pain, or any other indication the compounds

of the present invention are generally in a pharmaceutical composition so as to be administered to a subject at dosage levels of from 0.7 to 7000 mg per day, and preferably 1 to 500 mg per day, for a normal human adult of approximately 70 kg of body weight, this translates into a dosage of from 0.01 to 100 mg/kg of body weight per day. The specific dosages employed, however, can be varied depending upon the requirements of the patient, the severity of the condition being treated, and the activity of the compound being employed. The determination of optimum dosages for a particular situation is within the skill of the art.

The compounds of and combinatorial libraries containing the same can be prepared as set forth in Figures 1 to 4 and as described below.

Variant DHQ derivative combinatorial libraries can be prepared in order to achieve a high level of diversity. For instance, bromoacetic acid can be coupled (see Figures 1 to 4 and Example 1).

Other compounds can be loaded to solid support in various alternate ways. For example, a cleavable amino resin can be reacted with haloalkylesters, or by coupling the carboxylic acid group of diacid monoesters to a resin-bound amine via an amide bond (e.g., methylbenzhydrylamine (MBHA)). Alternatively, a hydroxyl resin (such a Wang resin) can be reacted with a caroboxylic acid, resulting in an ester linkage.

To the resulting compound can then be added an amine attached to an R group (see Figures 1 and 2 and Example 2). Alternatively, this step can be omitted (see

Figures 3 and 4 and Example 3). As another alternative, to the resulting compound can then be added -C(O)SH attached to an R group.

The resulting compound can then be reacted with a protected amino acid (see Example 3). Such a protected amino acid includes, for example, HO(OC)-CH_2-CH_2-NH-Fmoc (see Figures 1 and 3); HO(OC)-Ph-CH_2-NH-Boc (see Figures 2 and 4); and, in general, a compound of the formula HO(OC)-variable R moiety-NH-protecting group. Alternatively, the resulting compound can then be reacted with the corresponding amino halide (e.g., Br-Et-NH-Fmoc, Br-Ph-Me-NH-Boc or, in general, Br-variable R moiety-NH-protecting group), thus resulting in the same attached moiety without the carbonyl (i.e., where c of the claimed invention is 0). Alternatively, the resulting compound can then be reacted with the corresponding amino sulfonyl (e.g., leaving group-sulfonyl-variable R moiety-NH-protecting group), thus resulting in the same attached R moiety with sulfonyl replacing the carbonyl (i.e., where c of the claimed invention is -SO_2-). Once coupled, the amino moiety can then be deprotected (see Example 4).

The resulting compounds can then be reacted with an aldehyde (R variable group -CHO). See Example 5. Such a reaction results in the R_3 radical of the claimed invention (R_2 radical of Figures 1 to 4). Afterward, the compounds can be reacted with 4-nitrohomophthalic anhydride, resulting in the DHQ ring structure. See Example 6. The nitro group can then be reduced to an amino group by reaction with tin chloride. See Example 7.

The resulting compound can then be reacted with a carboxylic acid (R variable group -COOH). See Example 8. Such a reaction results in the R_2 and/or R_1 radical of the claimed invention (R_3 radical of Figures 1 to 4). Alternatively, the resulting compound can then be reacted with the corresponding halide (i.e., Br-variable R moiety), thus resulting in the same attached group without the carbonyl (i.e., where b of the claimed invention is 0). Alternatively, the resulting compound can then be reacted with the corresponding sulfonyl (e.g., leaving group-sulfonyl-variable R moiety), thus resulting in the same attached R moiety with sulfonyl replacing the carbonyl (i.e., where b of the claimed invention is $-SO_2-$).

Resin-bound DHQ derivative compounds can be cleaved by treating them, for example, with HF gas (see Example 9). The compounds can then be extracted, for example, with AcOH (see Example 10).

DHQ derivative compounds and libraries, such as those of the present invention, can be made utilizing individual polyethylene bags, referred to as "tea bags" (see Houghten et al., *Proc. Natl. Acad. Sci. USA* 82: 5131 (1985); *Biochemistry*, 32:11035 (1993); and U.S. Patent No. 4,631,211, all of which are incorporated herein by reference).

The nonsupport-bound combinatorial libraries can be screened as single compounds. In addition, the nonsupport-bound combinatorial libraries can be screened as mixtures in solution in assays such as radio-receptor inhibition assays, anti-bacterial assays, anti-fungal assays, calmodulin-dependent phosphodiesterase (CaMPDE)

assays and phosphodiesterase (PDE) assays, as described in detail below. Deconvolution of highly active mixtures can then be carried out by iterative or positional scanning methods. These techniques, the iterative approach or the positional scanning approach, can be utilized for finding other active compounds within the combinatorial libraries of the present invention using any one of the below-described assays or others well known in the art.

The iterative approach is well-known and is set forth in general in Houghten *et al.*, *Nature*, 354, 84-86 (1991) and Dooley *et al.*, *Science*, 266, 2019-2022 (1994), both of which are incorporated herein by reference. In the iterative approach, for example, sub-libraries of a molecule having three variable groups are made wherein the first variable is defined. Each of the compounds with the defined variable group is reacted with all of the other possibilities at the other two variable groups. These sub-libraries are each tested to define the identity of the second variable in the sub-library having the highest activity in the screen of choice. A new sub-library with the first two variable positions defined is reacted again with all the other possibilities at the remaining undefined variable position. As before, the identity of the third variable position in the sub-library having the highest activity is determined. If more variables exist, this process is repeated for all variables, yielding the compound with each variable contributing to the highest desired activity in the screening process. Promising compounds from this process can then be synthesized on larger scale in traditional single-compound synthetic methods for further biological investigation.

The positional-scanning approach has been described for various combinatorial libraries as described, for example, in R. Houghten *et al.* PCT/US91/08694 and U.S. Patent 5,556,762, both of which are incorporated herein by reference. In the positional scanning approach, sublibraries are made defining only one variable with each set of sublibraries and all possible sublibraries with each single variable defined (and all other possibilities at all of the other variable positions), made and tested. From the instant description one skilled in the art could synthesize combinatorial libraries wherein two fixed positions are defined at a time. From the testing of each single-variable defined combinatorial library, the optimum substituent at that position can be determined, pointing to the optimum or at least a series of compounds having a maximum of the desired biological activity. Thus, the number of sublibraries for compounds with a single position defined will be the number of different substituents desired at that position, and the number of all the compounds in each sublibrary will be the product of the number of substituents at each of the other variables.

Individual compounds and pharmaceutical compositions containing the compounds, as well as methods of using the same, are included within the scope of the present invention. The compounds of the present invention can be used for a variety of purposes and indications and as medicaments for any such purposes and indications. For example, DHQ derivative compounds of the present invention can be used as pesticides, acaricides, receptor agonists or antagonists and antimicrobial agents, including antibacterial or

antiviral agents. For example, the libraries can be screened in any variety of melanocortin receptor and related activity assays, such as those detailed below as well as others known in the art. Additionally, the subject compounds can be useful as analgesics. Assays which can be used to test the biological activity of the instant compounds include antimicrobial assays, a competitive enzyme-linked immunoabsorbent assay and radio-receptor assays, as described below.

The melanocortin (MC) receptors are a group of cell surface proteins that mediate a variety of physiological effects, including regulation of adrenal gland function such as production of the glucocorticoids cortisol and aldosterone; control of melanocyte growth and pigment production; thermoregulation; immunomodulation; and analgesia. Five distinct MC receptors have been cloned and are expressed in a variety of tissues, including melanocytes, adrenal cortex, brain, gut, placenta, skeletal muscle, lung, spleen, thymus, bone marrow, pituitary, gonads and adipose tissue (Tatro, Neuroimmunomodulation 3:259-284 (1996)). Three MC receptors, MCR-1, MCR-3 and MCR-4, are expressed in brain tissue (Xia et al., Neuroreport 6:2193-2196 (1995)).

A variety of ligands termed melanocortins function as agonists that stimulate the activity of MC receptors. The melanocortins include melanocyte-stimulating hormones (MSH) such as α-MSH, β-MSH and γ-MSH, as well as adrenocorticotropic hormone (ACTH). Individual ligands can bind to multiple MC receptors with differing relative affinities. The variety of ligands and MC receptors with differential

tissue-specific expression likely provides the molecular basis for the diverse physiological effects of melanocortins and MC receptors. For example, α-MSH antagonizes the actions of immunological substances such as cytokines and acts to modulate fever, inflammation and immune responses (Catania and Lipton, Annals N. Y. Acad. Sci. 680:412-423 (1993)).

The role of certain specific MC receptors in some of the physiological effects described above for MC receptors has been elucidated. For example, MCR-1 is involved in pain and inflammation. MCR-1 mRNA is expressed in neutrophils (Catania et al., Peptides 17:675-679 (1996)). The anti-inflammatory agent α-MSH was found to inhibit migration of neutrophils. Thus, the presence of MCR-1 in neutrophils correlates with the anti-inflammatory activity of α-MSH.

An interesting link of MC receptors to regulation of food intake and obesity has recently been described. The brain MC receptor MCR-4 has been shown to function in the regulation of body weight and food intake. Mice in which MCR-4 has been knocked out exhibit weight gain (Huszar et al., Cell 88:131-141 (1997)). In addition, injection into brain of synthetic peptides that mimic melanocortins and bind to MCR-4 caused suppressed feeding in normal and mutant obese mice (Fan et al., Nature 385:165-168 (1997)). These results indicate that the brain MC receptor MCR-4 functions in regulating food intake and body weight.

Due to the varied physiological activities of MC receptors, high affinity ligands of MC receptors could be used to exploit the varied physiological responses of

MC receptors by functioning as potential therapeutic agents or as lead compounds for the development of therapeutic agents. Furthermore, due to the effect of MC receptors on the activity of various cytokines, high affinity MC receptor ligands could also be used to regulate cytokine activity.

A variety of assays can be used to identify or characterize MC receptor ligands of the invention. For example, the ability of an DHQ derivative compound to compete for binding of a known MC receptor ligand can be used to assess the affinity and specificity of a DHQ compound for one or more MC receptors. Any MC receptor ligand can be used so long as the ligand can be labeled with a detectable moiety. The detectable moiety can be, for example, a radiolabel, fluorescent label or chromophore, or any detectable functional moiety so long as the MC receptor ligand exhibits specific MC receptor binding. A particularly useful detectable MC receptor ligand for identifying and characterizing other MC receptor ligands is ^{125}I-HP 467, which has the amino acid sequence Ac-Nle-Gln-His-(*p*(I)-D-Phe)-Arg-(D-Trp)-Gly-NH_2 and is described in Dooley et al., "Melanocortin Receptor Ligands and Methods of Using Same," U.S. patent application 09/027,108, filed February 20, 1998, which is incorporated herein by reference. HP 467 is a *para*-iodinated form of HP 228.

Using assay methods such as those described above, binding kinetics and competition with radiolabeled HP 467 can confirm that DHQ compounds of the invention bind to one or more MC receptors. Furthermore, DHQ derivative compounds of the invention can exhibit a range of affinities and specificity for various MC receptors.

The invention provides MC receptor ligands that can bind to several MC receptors with similar affinity. In addition, the invention also provides MC receptor ligands that can be selective for one or more MC receptors. As used herein, the term "selective" means that the affinity of a MC receptor ligand differs between one MC receptor and another by about 10-fold, generally about 20- to 50-fold, and particularly about 100-fold. In some cases, a MC receptor ligand having broad specificity is desired. In other cases, it is desirable to use MC receptor ligands having selectivity for a particular MC receptor. For example, MCR-1 ligands are particularly useful for treating pain and inflammation, whereas MCR-4 ligands are useful for treating obesity. The binding characteristics and specificity of a given MC receptor ligand can be selected based on the particular disease or physiological effect that is desired to be altered.

Another assay useful for identifying or characterizing MC receptor ligands measures signaling of MC receptors. MC receptors are G protein-coupled receptors that couple to adenylate cyclase and produce cAMP. Therefore, measuring cAMP production in a cell expressing a MC receptor and treated with a MC receptor ligand can be used to assess the function of the MC receptor ligand in activating a MC receptor.

Ligands for MC-3 that can alter the activity of an MC-3 receptor can be useful for treating sexual dysfunction and other conditions or conditions associated with MC-3 such as inflammation. Other MC-3-associated conditions that can be treated with the MC-3 receptor ligands include disuse deconditioning; organ damage such

as organ transplantation or ischemic injury; adverse reactions associated with cancer chemotherapy; diseases such as atherosclerosis that are mediated by free radicals and nitric oxide action; bacterial endotoxic sepsis and related shock; adult respiratory distress syndrome; and autoimmune or other patho-immunogenic diseases or reactions such as allergic reactions or anaphylaxis, rheumatoid arthritis, inflammatory bowel disease, ulcerative colitis, glomerulonephritis, systemic lupus erythematosus, transplant atherosclerosis and parasitic mediated immune dysfunctions such as Chagas's Disease.

The invention further provides a method for treating an MC-3-associated condition in a subject. The term "MC-3-associated condition" includes any condition or condition mediated by MC-3 or can be affected by binding an MC-3 ligand. Such conditions include inflammation and sexual dysfunction.

The term "sexual dysfunction" herein means any condition that inhibits or impairs normal sexual function, including coitus. However, the term need not be limited to physiological conditions, but may include psychogenic conditions or perceived impairment without a formal diagnosis of pathology.

In males, sexual dysfunction includes erectile dysfunction. The term "erectile dysfunction" or "impotence" means herein the inability or impaired ability to attain or sustain an erection that would be of satisfactory rigidity for coitus. Sexual dysfunction in males can also include premature ejaculation and priapism, which is a condition of prolonged and sometimes

painful erection unrelated to sexual activity, often associated with sickle-cell disease.

In females, sexual dysfunction includes sexual arousal disorder. The term "sexual arousal disorder" means herein a persistent or recurrent failure to attain or maintain the lubrication-swelling response of sexual excitement until completion of sexual activity. Sexual dysfunction in females can also include inhibited orgasm and dyspareunia, which is painful or difficult coitus. Sexual dysfunction can also be manifested as inhibited sexual desire or inhibited lordosis behavior in animals.

In addition, the ability of the compounds to inhibit bacterial growth, and therefore be useful to that infection, can be determined by methods well known in the art. Compounds of the present invention were shown to have antimicrobial activity by the *in vitro* antimicrobial activity assay described below and, therefore, are useful as antimicrobial agents (see Example 16).

In addition, an exemplary *in vitro* antimicrobial activity assay is described in Blondelle and Houghten, *Biochemistry* 30:4671-4678 (1991), which is incorporated herein by reference. In brief, *Staphylococcus aureus* ATCC 29213 (Rockville, MD) is grown overnight at 37°C in Mueller-Hinton broth, then re-inoculated and incubated at 37°C to reach the exponential phase of bacterial growth (i.e., a final bacterial suspension containing 10^5 to 5 x 10^5 colony-forming units/ml). The concentration of cells is established by plating 100 µl of the culture solution using serial dilutions (e.g., 10^{-2}, 10^{-3} and 10^{-4}) onto solid agar plates. In 96-well tissue culture plates, compounds,

individual or in mixtures, are added to the bacterial suspension at concentrations derived from serial two-fold dilutions ranging from 1500 to 2.9 µg/ml. The plates are incubated overnight at 37°C and the growth determined at each concentration by OD_{620} nm. The IC_{50} (the concentration necessary to inhibit 50% of the growth of the bacteria) can then be calculated.

The competitive ELISA method which can be used here is a modification of the direct ELISA technique described previously in Appel et al., J. Immunol. 144:976-983 (1990), which is incorporated herein by reference. It differs only in the MAb addition step. Briefly, multi-well microplates are coated with the antigenic peptide (Ac-GASPYPNLSNQQT-NH_2) at a concentration of 100 pmol/50 µl. After blocking, 25 µl of a 1.0 mg/ml solution of each mixture of a synthetic combinatorial library (or individual compound) is added, followed by MAb 125-10F3 (Appel et al., *supra*) (25 µl per well). The MAb is added at a fixed dilution in which the bicyclic guanidine in solution effectively competes for MAb binding with the antigenic peptide adsorbed to the plate. The remaining steps are the same as for direct ELISA. The concentration of compound necessary to inhibit 50% of the MAb binding to the control peptide on the plate (IC_{50}) is determined by serial dilutions of the compound.

Alternative screening can be done with radio-receptor assays. The radio-receptor assay, can be selective for any one of the µ, κ, or δ opiate receptors. Compounds of the present invention can be useful in vitro for the diagnosis of relevant opioid receptor subtypes, such as κ, in the brain and other tissue samples.

Similarly, the compounds can be used *in vivo* diagnostically to localize opioid receptor subtypes.

The radio-receptor assays are also an indication of the compounds' analgesic properties as described, for example, in Dooley et al., *Proc. Natl. Acad. Sci.*, 90:10811-10815 (1993). For example, it can be envisioned that these compounds can be used for therapeutic purposes to block the peripheral effects of a centrally acting pain killer. For instance, morphine is a centrally acting pain killer. Morphine, however, has a number of deleterious effects in the periphery which are not required for the desired analgesic effects, such as constipation and pruritus (itching). While it is known that the many compounds do not readily cross the blood-brain barrier and, therefore, elicit no central effect, the subject compounds can have value in blocking the periphery effects of morphine, such as constipation and pruritus. Accordingly, the subject compounds can also be useful as drugs, namely as analgesics, or to treat pathologies associated with other compounds which interact with the opioid receptor system.

Additionally, such compounds can be tested in a σ receptor assay. Ligands for the σ receptor can be useful as antipsychotic agents, as described in Abou-Gharbia et al., *Annual Reports in Medicinal Chemistry*, 28:1-10 (1993).

Radio-receptor assays can be performed with particulate membranes prepared using a modification of the method described in Pasternak et al., *Mol. Pharmacol.* 11:340-351 (1975), which is incorporated herein by reference. Rat brains frozen in liquid nitrogen can be

obtained from Rockland (Gilbertsville, PA). The brains are thawed, the cerebella removed and the remaining tissue weighed. Each brain is individually homogenized in 40 ml Tris-HCl buffer (50 mM, pH 7.4, 4°C) and centrifuged (Sorvall® RC5C SA-600: Du Pont, Wilmington, DE) (16,000 rpm) for 10 minutes. The pellets are resuspended in fresh Tris-HCl buffer and incubated at 37°C for 40 minutes. Following incubation, the suspensions are centrifuged as before, the resulting pellets resuspended in 100 volumes of Tris buffer and the suspensions combined. Membrane suspensions are prepared and used in the same day. Protein content of the crude homogenates generally range from 0.15-0.2 mg/ml as determined using the method described in Bradford, M.M., *Anal. Biochem.* 72:248-254 (1976), which is incorporated herein by reference.

Binding assays are carried out in polypropylene tubes, each tube containing 0.5 ml of membrane suspension. 8 nM of ^{3}H-[D-Ala^2,Me-Phe^4,Gly-ol^5]enkephalin (DAMGO) (specific activity = 36 Ci/mmol, 160,000 cpm per tube; which can be obtained from Multiple Peptide Systems, San Diego, CA, through NIDA drug distribution program 271-90-7302) and 80 µg/ml of bicyclic guanidine, individual or as a mixture and Tris-HCl buffer in a total volume of 0.65 ml. Assay tubes are incubated for 60 mins. at 25°C. The reaction is terminated by filtration through GF-B filters on a Tomtec harvester (Orange, CT). The filters are subsequently washed with 6 ml of Tris-HCl buffer, 4°C. Bound radioactivity is counted on a Pharmacia Biotech Betaplate Liquid Scintillation Counter (Piscataway, NJ) and expressed in cpm. To determine inter- and intra-assay variation, standard curves in which ^{3}H-DAMGO is incubated in the presence of a range of

concentrations of unlabeled DAMGO (0.13-3900 nM) are generally included in each plate of each assay (a 96-well format). Competitive inhibition assays are performed as above using serial dilutions of the bicyclic guanidines, individually or in mixtures. IC_{50} values (the concentration necessary to inhibit 50% of ^3H-DAMGO binding) are then calculated. IC_{50} values of less than 1000 nM are indicative of highly active opioid compounds which bind to the μ receptor, with particularly active compounds having IC_{50} values of 100 nM or less and the most active compounds with values of less than 10 nM.

As opposed to this μ receptor selective assay, which can be carried out using ^3H-DAMGO as radioligand, as described above, assays selective for κ receptors can be carried out using [^3H]-U69,593 (3 nM, specific activity 62 Ci/mmol) as radioligand. Assays selective for δ opiate receptors can be carried out using tritiated DSLET ([D-Ser^2, D-Leu^5]-threonine-enkephalin) as radioligand. Assays selective for the σ opiate receptor can use radiolabeled pentazocine as ligand.

Screening of combinatorial libraries and compounds of the invention can be done with an anti-fungal assay. Compounds of the present invention can be useful for treating fungal infections.

Screening of combinatorial libraries and compounds of the invention also can be done with a calmodulin-dependent phosphodiesterase (CaMPDE) assay. Compounds of the present invention can be useful as calmodulin antagonists.

Calmodulin (CaM), which is the major intracellular calcium receptor, is involved in many processes that are crucial to cellular viability. In particular, calmodulin is implicated in calcium-stimulated cell proliferation. Calmodulin antagonists are, therefore, useful for treating conditions associated with increased cell proliferation, for example, cancer. In addition, calmodulin antagonists such as compounds of the subject invention are useful both in vitro and in vivo for identifying the role of calmodulin in other biological processes. The disadvantages of known antagonists such as trifluoperazine and N-(4-aminobutyl)-5-chloro-2-naphthalenesulfonamide (W13) include their non-specificity and toxicity. In contrast, advantages of the combinatorial libraries and compounds of the subject invention as calmodulin antagonists include their reduced flexibility and ability to generate broader conformational space of interactive residues as compared to their linear counterparts.

An example of an assay that identifies CaM antagonists is a CaMPDE assay. In brief, samples are mixed with 50 µl of assay buffer (360 mM Tris, 360 mM Imidazole, 45 mM $Mg(CH_3COO)_2$, pH 7.5) and 10 µl of $CaCl_2$ (4.5 mM) to a final volume of 251 µl. 25 µl of calmodulin stock solution (Boehringer Mannheim; 0.01 µg/µl) is then added and the samples then sit at room temperature for 10 minutes. 14 µl of PDE (Sigma; 2 Units dissolved in 4 ml of water; stock concentration: 0.0005 Units/µl) is then added, followed by 50 µl of 5'-nucleotidase (Sigma; 100 Units dissolved in 10 ml of 10 mM Tris-HCl containing 0.5 mM $Mg(CH_3COO)_2$, pH 7.0; stock concentration: 10 Units/ml). The samples are then incubated for 10 minutes at 30°C. 50 µl of adenosine

3',5'-cyclic monophosphate (cAMP) (20 mM in water at pH 7.0) is added, the samples incubated for 1 hour at 30°C and then vortexed. 200 µl of trichloroacetic acid (TCA) (55% in water) is added to a 200 µl sample aliquot, which is then vortexed and centrifuged for 10 minutes. 80 µl of the resulting supernatants of each sample is transferred to a 96-well plate, with 2 wells each containing 80 µl of each sample. 80 µl of ammonium molybdate (1.1% in 1.1N H_2SO_4) is then added to all the wells, and the OD of each were determined at 730nm, with the values later subtracted to the final OD reading. 16 µl of reducing agent (6g sodium bisulfite, 0.6g sodium sulfite and 125mg of 1-amino-2-naphtol-4-sulfonic acid in 50ml of water) is then added to one of each sample duplicate and 16 µl of water is added to the other duplicate. After sitting for 1 hour at room temperature, the OD of each well is determined at 730nm. The percent inhibition of calmodulin activity is then calculated for each sample, using as 0% inhibition a control sample containing all reagents without any test samples and as 100% inhibition a control sample containing test samples and all reagents except calmodulin. In addition, the percent inhibition of phosphodiesterase activity was determined by following a similar protocol as the CaMPDE assay described above, except not adding calmodulin to the sample mixture and calculating the percent inhibition by using as 0% inhibition a control reagent without any test samples and as 100% inhibition a control sample containing test samples and all reagents except cAMP.

The following examples are provided to illustrate but not limit the present invention. In the examples, the following abreviations have the corresponding meanings:

MBHA : 4-methylbenzhydrylamine;
DMF : dimethylforamide;
HoBt : 1-hydroxybenzotriazole;
DMSO : dimethylsulfoxide;
Boc : tert-butoxycarbonyl;
FMOC : 9-fluorenyl-methoxycarbonyl;
DMAP : 4-dimethylamino-pyridine;
DIC : N,N'-diisopropylcarbodiimide;
TFA : trifluoroacetic acid;
DIEA : diisopropylethylamine;
DCM : dichloromethane;
TMOF: trimethylorthoformate;
HATU : azabenzotriazolyl-N,N,N',N'-tetramethyluronium hexafluorophosphate;

EXAMPLE 1

Bromoacetic Acid Coupling:

MBHA resin containing Tbags (1.25g x 1.2 mmol/g per bag) were placed into Nalgene bottles (40 bags per 2L bottle) and washed with DMF (1X,700mL, 20 min), washed with 50% piperidine/DMF (1X, 700 mL for 2L bottle, 20 min), washed with DMF (4X, 700 mL), washed with 0.3M HoBt/DMF (1X, 700 mL) and finally washed with DMF (4X, 700mL) containing 1mL of 1% bromophenol blue in the last wash only. A bromoacetic acid/DMF solution (0.7 mol, 700mL) was prepared and to this was added DIC (0.84 mol) and the mixture was stirred for about 30 seconds, then poured into the 2L bottle containing the Tbags immediately. The reaction was shaken at room temperature for 1 hour (2 hours maximum).

EXAMPLE 2

R1-Amine Coupling:

The Tbags from the reaction described in Example 1 were washed with DMF (3X, 500mL), with DMSO (2X, 500mL). The appropriate number of R1amine/DMSO solutions (1.0 mol of amine, 1000mL of DMSO) were prepared and placed in 2L Nalgene bottles with the appropriate Tbags (40 bags per bottle). The reactions were shaken overnight at room temperature.

EXAMPLE 3

Amino Acid Coupling:

The Tbags from the reaction above were washed with DMSO (1X, 500mL), and with DMF (5X, 500mL) containing 0.5 mL of 1% bromophenol blue in the last wash only.

The amino acid/DMF solutions were prepared by dissolving 0.3 moles of HOBt in approximately 900mL of DMF and adding to these solutions the amino acids (0.3 moles) containing the appropriate protecting group of either BOC or Fmoc. To these solutions were added DMAP (3.7 gm)and DIC(47.0mL) right before use and finally the total volume for each solution was adjusted to 1000mL using DMF. The Tbags were placed into 2L Nalgene bottles (60 bags per bottle), then the amino acid solutions prepared as above were added. The reactions were shaken overnight at room temperature. The Tbags were washed with DMF (2X 500mL), MeOH (2X 500mL), DMF (2X 500mL), MeOH (2X 500mL), DCM (2X 500mL), and finally with MeOH (2X, 500mL) and air dried in fume hood overnight.

A similar procedure as that described above in Example 3 was followed on a fraction of the bags directly from bromoacetic acid coupling step (as described in Example 1) without further R1 coupling (which is described in Example 2).

EXAMPLE 4

Amino Acid Deprotection:

a. Boc Deprotection:

The appropriate Tbags were placed into 2L Nalgene bottles (50 bags per 2L bottle) and washed with DCM (1X, 1000mL, 20 min), then shaken with 55% TFA/DCM for 1 hour (1000mL, add slowly). The TFA solution was poured out and the Tbags were washed with DCM (3X, 1000mL), with 5% DIEA/DCM (2X, 1000mL), with DCM (3X, 1000mL), with DMF (2X, 1000mL), with 50% piperidine/DMF (1X, 1000 mL, 20 min), and finally with DMF (5X, 1000mL).

b. Fmoc Deprotection:

The appropriate Tbags were placed into 2L Nalgene bottles (50 bags per 2L bottle) and washed with DMF (1X, 1000mL, 20 min), then washed with 50% piperidine/DMF for 30 minutes (1000mL). The piperidine solution was poured out and the Tbags were washed with DMF (5X, 1000mL).

EXAMPLE 5

R2-Aldehyde Reaction:

To the appropriate Tbags (50 bags per 2L bottle), a 1L solution containing 0.4 moles of aldehyde and 0.8 moles of TMOF in DMF was prepared and added. The reactions were shaken 33.5 hours at room temperature. The T-bags were washed with 0.2 M TMOF solution in DMF (2X 500mL).

EXAMPLE 6

4-Nitrohomophthalic anhydride Reaction:

Following the above wash step, a 0.4 M solution of 4-nitrohomophthalic anhydride in DMF was prepared containing 0.03 M DIEA and then added to the Tbags immediately (50 bags per 2L bottle). The reactions were shaken overnight at room temperature.

The Tbags were washed with DMF (6X, 500mL), MeOH (2X, 500mL), DMF (2X, 500mL), MeOH (2X, 500mL), DCM (3X, 500mL), and MeOH (3X, 500mL). The Tbags were air dried bags overnight.

EXAMPLE 7

Tin Chloride Reduction:

The Tbags were placed in 2L bottles (100 bags per 2L bottle). A 2 M solution of tin chloride dihydrate in DMF was prepared and added to the reaction bottles (1L per bottle) containing the T-bags. The reactions were shaken overnight for 24 hours.

The Tbags were washed with DMF (6X, 500mL), MeOH (3X, 500mL), DMF (3X, 500mL), 5% DIEA/DCM (3X, 500mL),

DCM (3X, 500mL), and MeOH (3X, 500mL). The Tbags were air dried overnight.

EXAMPLE 8

Carboxylic Acid Coupling:

The resin from each Tbag was placed into 48 wells of a 96 well microtiter plate (~26 mg per well). All wells were washed with DMF (2X, 1.0mL). Each carboxylic acid solution was prepared to contain 0.5 M carboxylic acid, 0.5 M HATU, and 1.0 M DIEA in DMF. These solution mixtures were then shaken for 20 minutes before addition to the plates. The required 48 different carboxylic acid solutions were added to each appropriate well (0.5mL/well). The microtiter plates were capped and shaken at rt overnight. The resin in each well was washed with DMF (2X, 1.0mL per well). This procedure was repeated to affect a double coupling of the amine to the resin bound carboxylic acid.

The wells on all plates were washed with DMF (8X, 1.0mL), with MeOH (4X, 1.0mL), with DMF (4X, 1.0mL), and with MeOH (6X, 1.0mL). The plates were air dried in a fume hood for three days.

EXAMPLE 9

Gaseous HF Cleavage:

The plates in batches of ~15 were treated by passing N2 through chamber for 30 min, then passing HF gas for 15 min. The chamber was isolated under HF for 1.5 h, then the HF was removed by passing N2 through the chamber overnight. The plates were removed and the residual HF removed under vacuum in desiccators overnight.

EXAMPLE 10

AcOH Extraction:

To extract the cleaved compound from the spent resin, 0.7 mL of AcOH was added into each well and shaken for 20 min. Extraction of each well was accomplished with 2x0.7 mL of AcOH per well to yield the final compound in acetic acid solution. The acetic acid was removed by lyophilization.

EXAMPLE 11

Preparation of a combinatorial library of DHQ derivative compounds

Bromoacetic acid was coupled to resin contained in Tbags, as described in Example 1. In accord with Example 2, the resulting resin-bound compound in an individual Tbag was coupled with one of 24 amine-containing compounds selected from the following list:

1-(2-aminoethyl)piperidine
1-(3-aminopropyl)imidazole
2,4-dichlorophenethylamine
2-(2-aminoethyl)pyridine
3-(aminomethyl)pyridine
3-(trifluoromethyl)benzylamine
3-ethoxypropylamine
4-(2-aminoethyl)morpholine
acethydrazide
allylamine
benzylamine
cyclopropylamine
methylhydrazinocarboxylate
N,N-dinbutylethylenediamine

N,N-dimethylethylenediamine
piperazine
propylamine
2-(4-methoxyphenyl)ethylamine
cyclohexanemethylamine
3-diethylaminopropyldiamine
1-amino-4-methylpiprazine
3-methoxybenzylamine
2-(aminomethyl)-1-ethyl-pyrrolidine
2-methoxyethylamine

As described in Example 3, the resulting compounds were coupled with Fmoc-NH-Et-COOH, deprotected (as described in Example 4) and, subsequently, (as described in Example 5) reacted with one of the following 20 aldehydes:

benzaldehyde
1-naphthaldehyde
3-cyanobenzaldehyde
2-imidazolecarboxaldehyde
2-pyridinecarboxaldehyde
3-pyridinecarboxaldehyde
2-quinolinecarboxaldehyde
4-methylbenzaldehyde
4-(3-dimethylaminopropoxy)benzaldehyde
4-(methylthio)benzaldehyde
4-(trifluoromethyl)benzaldehyde
3,5-dimethoxybenzaldehyde
3,4-difluorobenzaldehyde
4-tert-butylbenzaldehyde
4-acetamidobenzaldehyde
3-(3,4-dichlorophenoxy)benzaldehyde
2-fluorenecarboxaldehyde
4-(dimethylamino)cinnamaldehyde
4-(dimethylamino)benzaldehyde

iso-butyraldehyde

The resulting compounds were then reacted with 4-nitrohomophthalic acid, as described in Example 6, and reduced with tin chloride, as described in Example 7.

Afterwards, as described in Example 8, the compounds were reacted with one of the following 48 carboxylic acids:

4-(trifluoromethoxy)benzoic acid
2,6-difluorobenzoic acid
2-pyrazinecarboxylic acid
2-furoic acid
2,3,5,6-tetrafluoro-p-toluic acid
3,4-difluorobenzoic acid
4-formylphenoxyacetic acid
2-(trifluoromethyl)cinnamic acid
diethylphosphonoacetic acid
2-fluoro-3-(trifluoromethyl)benzoic acid
2-fluorobenzoic acid
4-cyanobenzoic acid
4-acetylphenoxyacetic acid
1-phenyl-1-cyclopropanecarboxylic acid
phthalide-3-acetic acid
mesitylglyoxylic acid
6-methylchromone-2-carboxylic acid
2-naphthoxyacetic acid
3,5-bis(trifluoromethyl)benzoic acid
2-chloronicotinic acid
fumaric acid monoethyl ester
2-methylpyrazine-5-carboxylic acid
2-bromo-5-methoxybenzoic acid
4-iodobenzoic acid
2-bromobenzoic acid
4-methyl-1,2,3-thiadiazole-5-carboxylic acid

3,4,5-trimethoxycinnamic acid
2-(methylthio)benzoic acid
3-(trifluoromethyl)phenylacetic acid
2-methylcyclopropanecarboxylic acid
2-methylvaleric acid
methoxyacetic acid
2-propylpentanoic acid
3,5,5-trimethylhexanoic acid
vinylacetic acid
3-cyclopentylpropionic acid
hexanoic acid
tetrahydrofuran-2-carboxylic acid
2-nonenoic acid
3-cyclohexylpropionic acid
octanoic acid
3-methoxycyclohexanecarboxylic acid
4-methyl-1-cyclohexanecarboxylic acid
3-methylthiopropionic acid
3-methoxypropionic acid
cyclopentylacetic acid
2-norbornaneacetic acid
(methylthio)acetic acid

The resulting compounds were then cleaved and extracted, as described in Examples 9 and 10.

EXAMPLE 12

Preparation of a combinatorial library of DHQ derivative compounds

Bromoacetic acid was coupled to resin contained in Tbags, as described in Example 1. In accord with Example 2, the resulting resin-bound compound was coupled with one of 24 amine-containing compounds described in Example 11. As described in Example 3, the resulting compounds were coupled with 1,4-Boc-NH-CH_2-Ph-COOH (as shown in Figure 2), deprotected (as described in Example 4) and, subsequently, (as described in Example 5) reacted with one of the following 20 aldehydes listed in Example 11.

The resulting compounds were then reacted with 4-nitrohomophthalic acid, as described in Example 6, and reduced with tin chloride, as described in Example 7.

Afterwards, as described in Example 8, the compounds were reacted with one of the following 48 carboxylic acids listed in Example 11. The resulting compounds were then cleaved and extracted, as described in Examples 9 and 10.

EXAMPLE 13

Preparation of a combinatorial library of DHQ derivative compounds

Bromoacetic acid was coupled to resin contained in Tbags, as described in Example 1. As described in Example 3, the resulting compounds were coupled with Fmoc-NH-CH_2-CH_2-COOH (as shown in Figure 3), deprotected (as described in Example 4) and, subsequently, (as

described in Example 5) reacted with one of the following 20 aldehydes listed in Example 11.

The resulting compounds were then reacted with 4-nitrohomophthalic acid, as described in Example 6, and reduced with tin chloride, as described in Example 7.

Afterwards, as described in Example 8, the compounds were reacted with one of the following 48 carboxylic acids listed in Example 11. The resulting compounds were then cleaved and extracted, as described in Examples 9 and 10.

EXAMPLE 14

Preparation of a combinatorial library of DHQ derivative compounds

Bromoacetic acid was coupled to resin contained in Tbags, as described in Example 1. As described in Example 3, the resulting compounds were coupled with 1,4-Boc-NH-CH_2-Ph-COOH (as shown in Figure 4), deprotected (as described in Example 4) and, subsequently, (as described in Example 5) reacted with one of the following 20 aldehydes listed in Example 11.

The resulting compounds were then reacted with 4-nitrohomophthalic acid, as described in Example 6, and reduced with tin chloride, as described in Example 7.

Afterwards, as described in Example 8, the compounds were reacted with one of the following 48 carboxylic acids listed in Example 11. The resulting

compounds were then cleaved and extracted, as described in Examples 9 and 10.

EXAMPLE 15

Melanocortin Receptor Assay

This example describes methods for assaying binding to MC receptors.

All cell culture media and reagents were obtained from GibcoBRL (Gaithersburg MD), except for COSMIC CALF SERUM (HyClone; Logan UT). HEK 293 cell lines were transfected with the human MC receptors hMCR-1, hMCR-3, and hMCR-4 (Gantz et al., Biochem. Biophys. Res. Comm. 200:1214-1220 (1994); Gantz et al., J. Biol. Chem. 268:8246-8250 (1993); Gantz et al. J. Biol. Chem. 268:15174-15179 (1993); Haskell-Leuvano et al., Biochem. Biophys. Res. Comm. 204:1137-1142 (1994); each of which is incorporated herein by reference). Vectors for construction of an hMCR-5 expressing cell line were obtained, and a line of HEK 293 cells expressing hMCR-5 was constructed (Gantz, *supra*, 1994). hMCR-5 has been described previously (Franberg et al., Biochem. Biophys. Res. Commun. 236:489-492 (1997); Chowdhary et al., Cytogenet. Cell Genet. 68:1-2 (1995); Chowdhary et al., Cytogenet. Cell Genet. 68:79-81 (1995), each of which is incorporated herein by reference). HEK 293 cells were maintained in DMEM, 25 mM HEPES, 2 mM glutamine, non-essential amino acids, vitamins, sodium pyruvate, 10% COSMIC CALF SERUM, 100 units/ml penicillin, 100 μg/ml streptomycin and 0.2 mg/ml G418 to maintain selection.

Before assaying, cells were washed once with phosphate buffered saline ("PBS"; without Ca^{2+} and Mg^{2+}),

and stripped from the flasks using 0.25% trypsin and 0.5 mM EDTA. Cells were suspended in PBS, 10% COSMIC CALF SERUM and 1 mM $CaCl_2$. Cell suspensions were prepared at a density of $2x10^4$ cells/ml for HEK 293 cells expressing hMCR-3, hMCR-4 or hMCR-5, and $1x10^5$ cells/ml for HEK 293 cells expressing hMCR-1. Suspensions were placed in a water bath and allowed to warm to 37°C for 1 hr.

Binding assays were performed in a total volume of 250 µl for HEK 293 cells. Control and test compounds were dissolved in distilled water. ^{125}I-HP 467 (50,000 dpm) (2000 Ci/mmol) (custom labeled by Amersham; Arlington Heights IL) was prepared in 50 mM Tris, pH 7.4, 2 mg/ml BSA, 10 mM $CaCl_2$, 5 mM $MgCl_2$, 2 mM EDTA and added to each tube. To each tube was added $4x10^3$ HEK 293 cells expressing hMCR-3, hMCR-4 or hMCR-5, or $2x10^4$ cells expressing hMCR-1. Assays were incubated for 2.5 hr at 37°C.

GF/B filter plates were prepared by soaking for at least one hour in 5 mg/ml BSA and 10 mM $CaCl_2$. Assays were filtered using a Brandel 96-well cell harvester (Brandel Inc.; Gaithersburg, MD). The filters were washed four times with cold 50 mM Tris, pH 7.4, the filter plates were dehydrated for 2 hr and 35 µl of MICROSCINT was added to each well. Filter plates were counted using a Packard Topcount (Packard Instrument Co.) and data analyzed using GraphPad PRISM v2.0 (GraphPad Software Inc.; San Diego CA) and Microsoft EXCEL v5.0a (Microsoft Corp.; Redmond WA).

To assay DHQ derivative compounds, binding assays were performed in duplicate in a 96 well format. HP 467 was prepared in 50 mM Tris, pH 7.4, and ^{125}I-HP 467 was diluted to give 100,000 dpm per 50 µl. A DHQ derivative

compound, synthesized as described in Examples 11 to 14, was added to the well in 25 μl aliquots. A 25 μl aliquot of ^{125}I-HP 467 was added to each well. A 0.2 ml aliquot of suspended cells was added to each well to give the cell numbers indicate above, and the cells were incubated at 37°C for 2.5 hr. Cells were harvested on GF/B filter plates as described above and counted.

EXAMPLE 16

Anti-microbial Screen

Streptococcus pyogenes (ATCC# 97-03 14289) are grown in Todd Hewitt Broth (THB) (Difco Laboratories #0492-17-6) overnight until they reach an optical density of (OD = 0.636@ 570 nm) by reading 0.1 ml in a 96 well microtiter plate in a Molecular Devices Thermomax. This preparation is kept frozen as stocks in 30% v/v glycerol in 1.5 ml aliquots at -70 C° until use. Prior to screening, 1.5 ml aliquots are thawed and diluted into 50 ml THB. 200 ul of this dilution is added to 92 wells of microtiter plate. To three wells THB (200 ul) is added to serve as a blank and a sterility control. Test compounds in DMSO and appropriate concentrations of DMSO are added to Growth/Solvent Controls at 0 time. Plates are read at 0 time at 570 nm in the Molecular Devices plate reader to obtain compounds correction factors for insoluble or colored compounds. Plates are read again at 4 hrs.

Compounds are assayed at a concentration of 170 μg/ml. Percent inhibition for each compound is calculated using the following formulae:

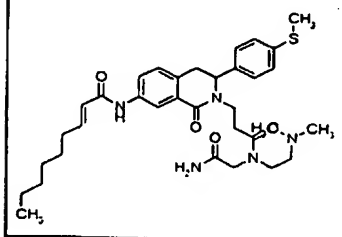
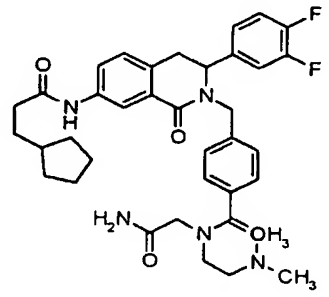
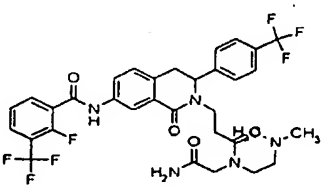
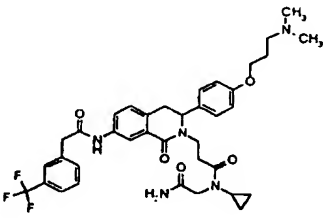
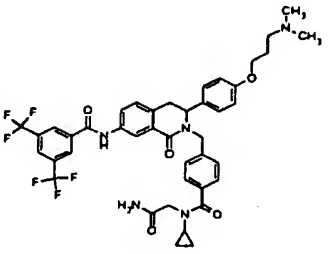
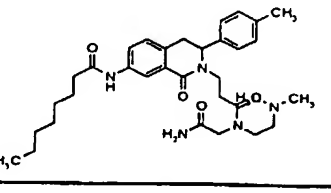
Color correct =

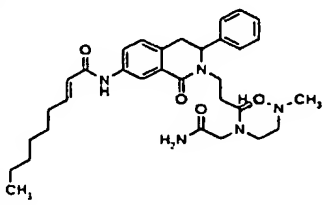
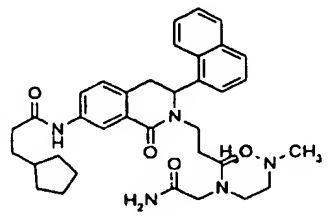
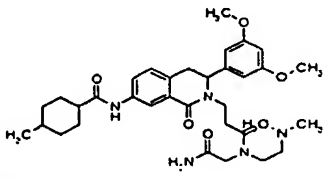
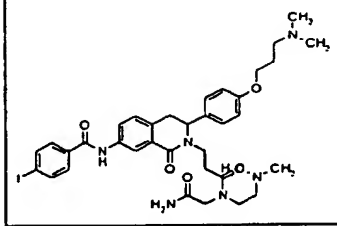
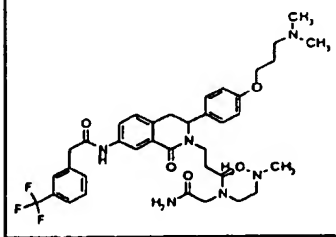
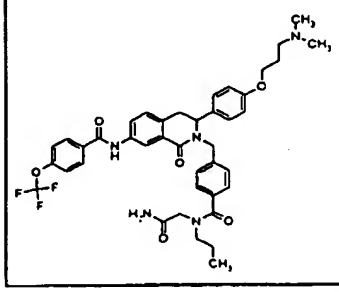
(O.D. 0 hr - Blank 0 hr)-(Solvent Control 0 hr - Blank 0 hr)

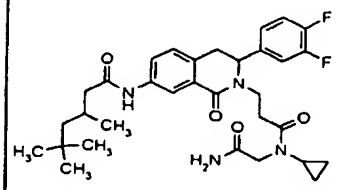
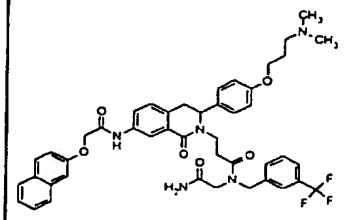
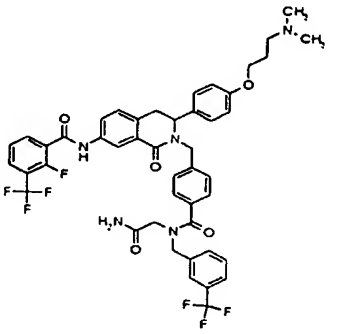
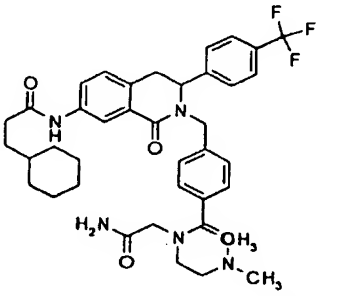
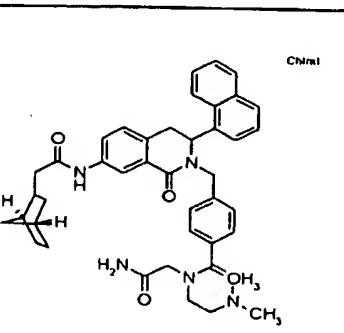
% Inhibition =

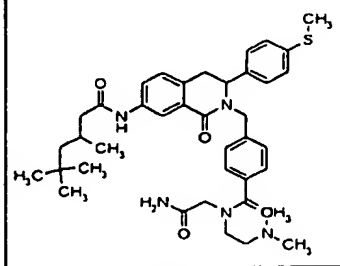
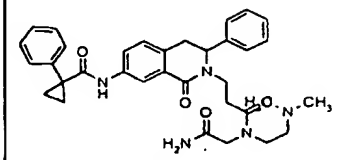
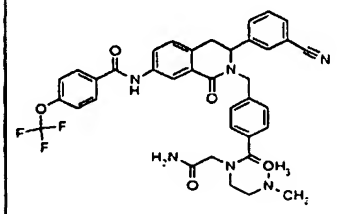
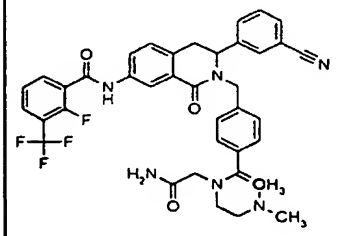
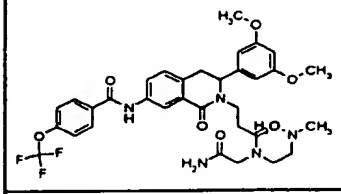
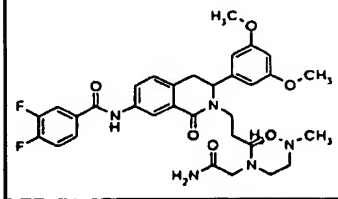
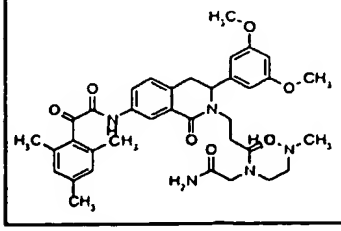
100 - (O.D. test compound 4 hr - Blank 4 hr - color correct) divided by (O.D. growth/solvent control 4 hr - Blank 4 hr)

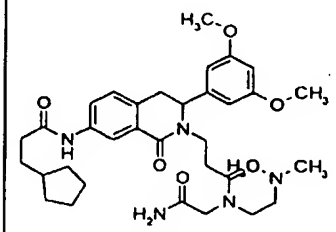
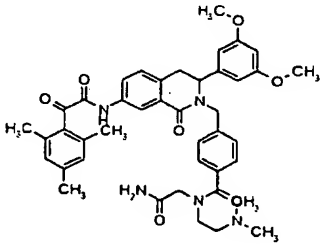
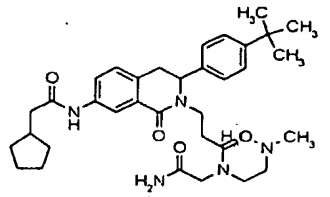
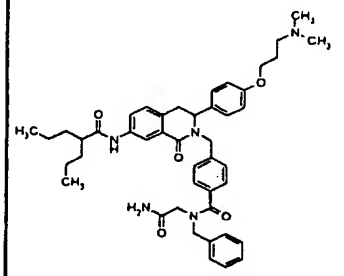
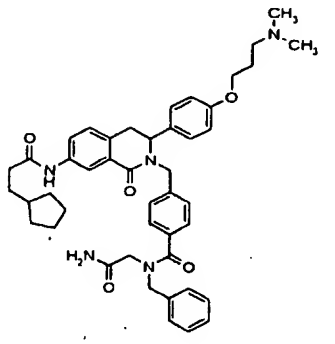
Percent inhibition of DHQ compounds of the invention are provided in the table below:

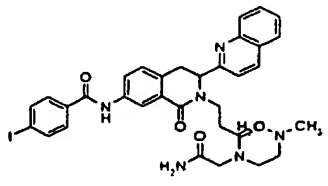
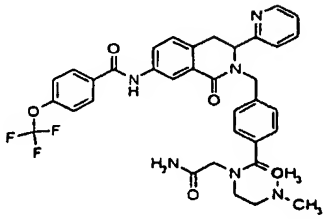
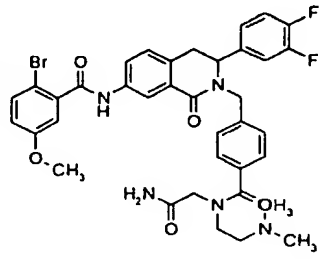
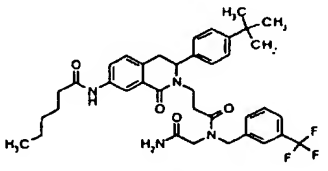
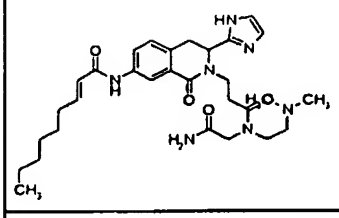
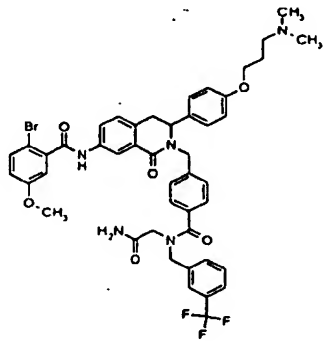
Molecular Structure	Molecular Formula	Molecular Weight	% Inhibition
	$C_{34}H_{47}N_5O_4S$	621.8423	99.93
	$C_{37}H_{43}F_2N_5O_4$	659.7737	99.93
	$C_{33}H_{32}F_7N_5O_4$	695.6328	99.88
	$C_{37}H_{42}F_3N_5O_5$	693.7628	99.88
	$C_{42}H_{41}F_6N_5O_5$	809.8039	99.88
	$C_{33}H_{47}N_5O_4$	577.7653	99.87

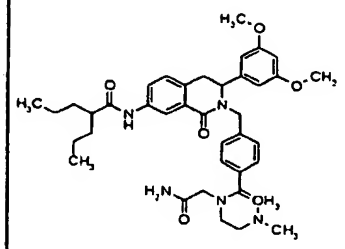
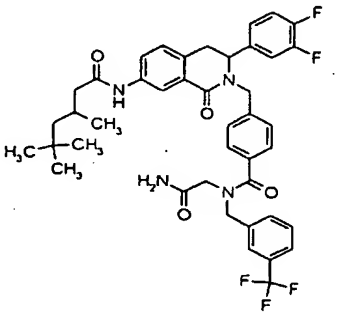
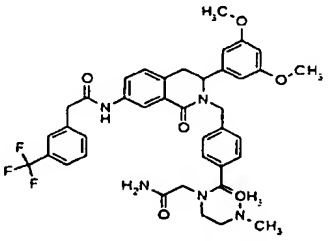
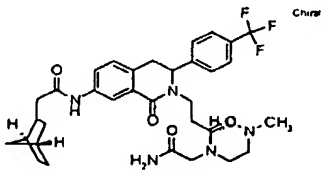
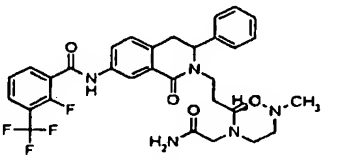
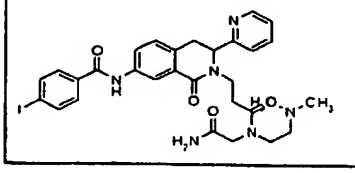
	$C_{33}H_{45}N_5O_4$	575.7495	99.85
	$C_{36}H_{45}N_5O_4$	611.7825	99.80
	$C_{34}H_{47}N_5O_6$	621.7743	99.80
	$C_{36}H_{45}IN_6O_5$	768.6885	99.76
	$C_{38}H_{47}F_3N_6O_5$	724.8203	99.76
	$C_{41}H_{44}F_3N_5O_6$	759.8216	99.68

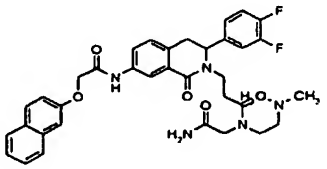
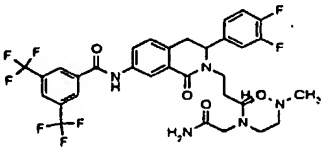
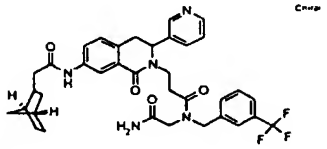
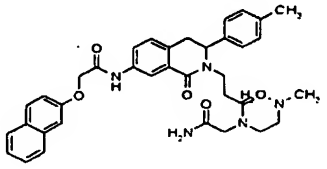
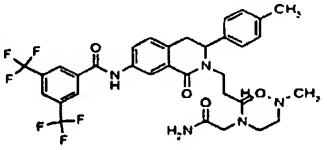
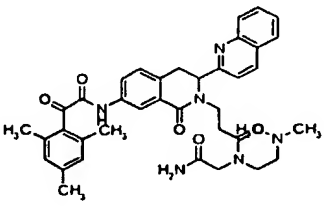
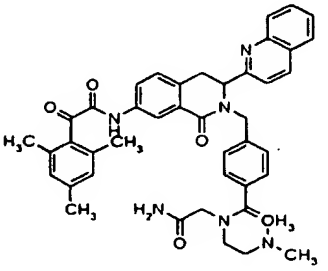
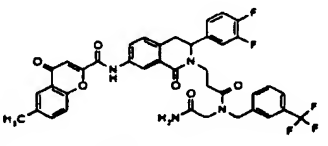
	$C_{32}H_{40}F_2N_4O_4$	582.688	99.67
	$C_{45}H_{46}F_3N_5O_6$	809.8814	99.63
	$C_{46}H_{42}F_7N_5O_5$	877.8538	99.63
	$C_{39}H_{46}F_3N_5O_4$	705.8174	99.63
	$C_{42}H_{47}N_5O_4$	685.8643	99.55

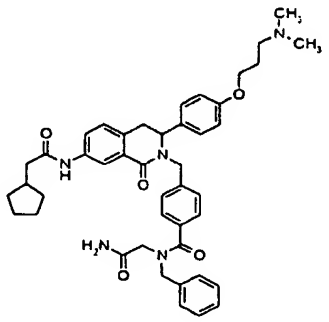
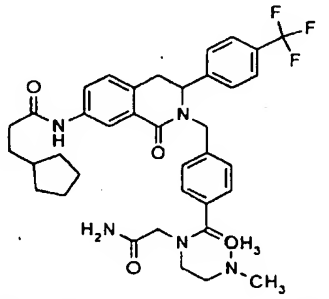
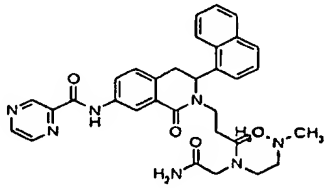
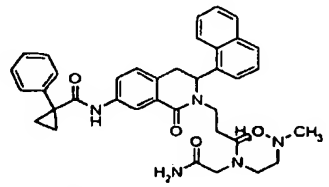
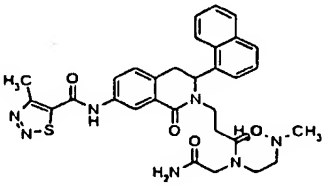
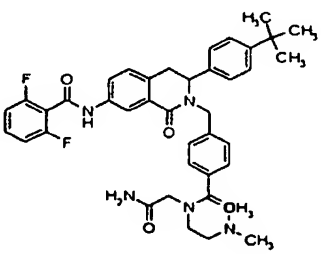
	$C_{39}H_{51}N_5O_4S$	685.9289	99.55
	$C_{34}H_{39}N_5O_4$	581.7131	99.55
	$C_{38}H_{35}F_3N_6O_5$	712.7255	99.54
	$C_{38}H_{34}F_4N_6O_4$	714.7166	99.54
	$C_{34}H_{38}F_3N_5O_7$	685.6962	99.52
	$C_{33}H_{37}F_2N_5O_6$	637.6803	99.52
	$C_{37}H_{45}N_5O_7$	671.7905	99.52

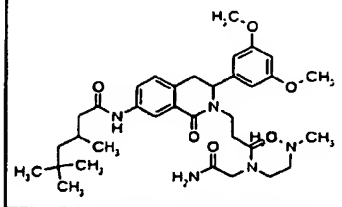
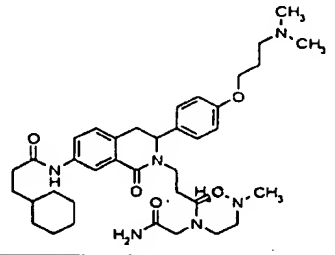
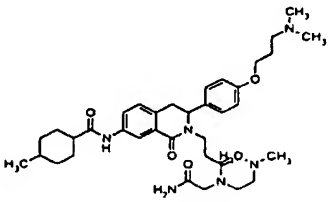
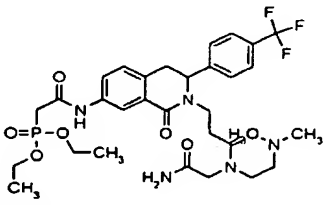
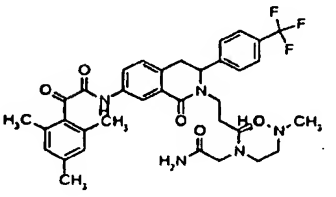
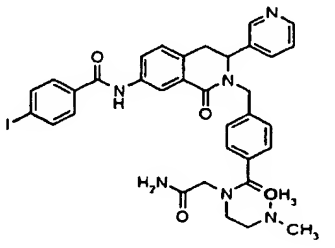
	$C_{34}H_{47}N_5O_6$	621.7743	99.52
	$C_{42}H_{47}N_5O_7$	733.8613	99.52
	$C_{35}H_{49}N_5O_4$	603.8031	99.51
	$C_{45}H_{55}N_5O_5$	745.9595	99.47
	$C_{45}H_{53}N_5O_5$	743.9437	99.47

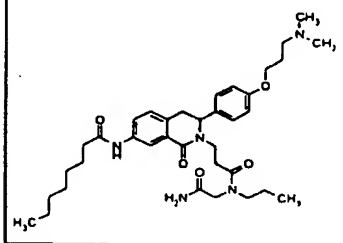
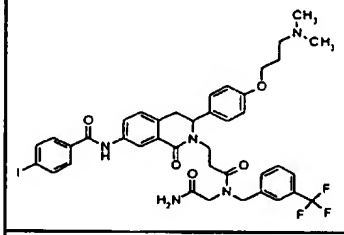
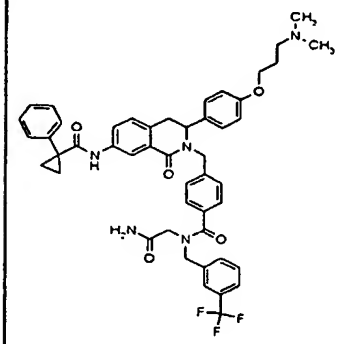
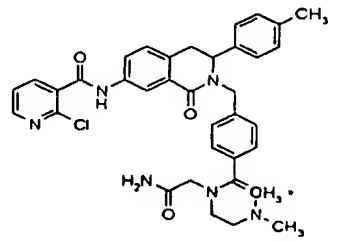
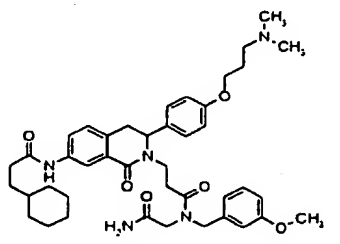
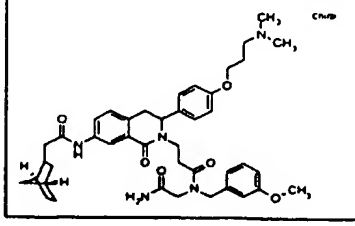
	$C_{34}H_{35}IN_6O_4$	718.5885	99.46
	$C_{36}H_{35}F_3N_6O_5$	688.7035	99.46
	$C_{37}H_{36}BrF_2N_5O_5$	748.6214	99.45
	$C_{38}H_{45}F_3N_4O_4$	678.7915	99.44
	$C_{30}H_{43}N_7O_4$	565.7147	99.38
	$C_{46}H_{45}BrF_3N_5O_6$	900.7885	99.36

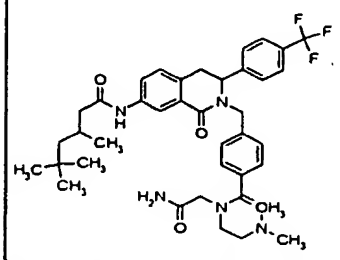
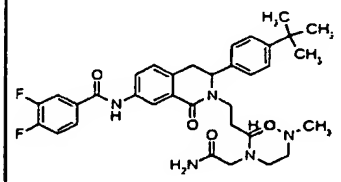
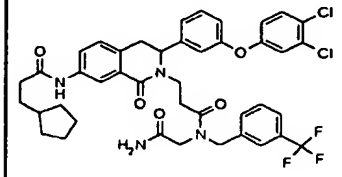
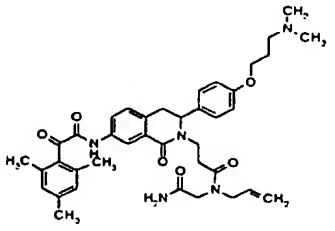
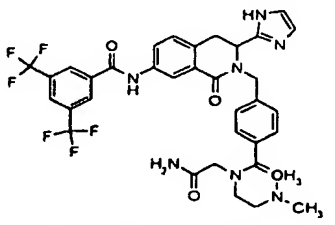
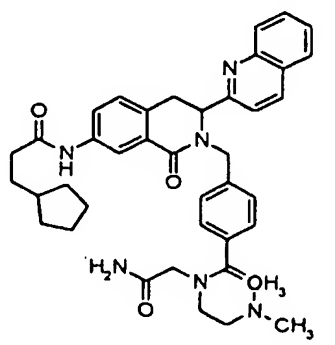
	$C_{39}H_{51}N_5O_6$	685.8609	99.33
	$C_{42}H_{43}F_5N_4O_4$	762.8157	99.30
	$C_{40}H_{42}F_3N_5O_6$	745.7948	99.25
	$C_{34}H_{42}F_3N_5O_4$	641.7308	99.25
	$C_{32}H_{33}F_4N_5O_4$	627.6357	99.25
	$C_{30}H_{33}IN_6O_4$	668.5287	99.18

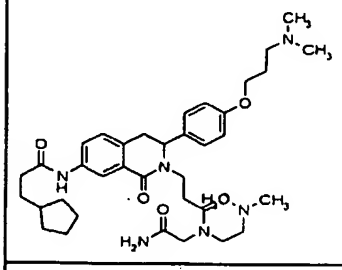
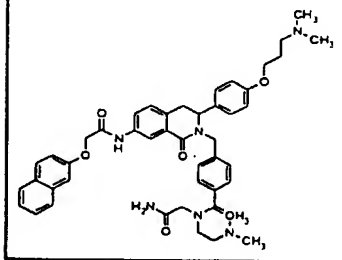
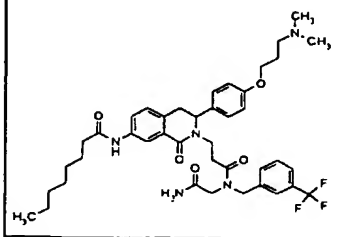
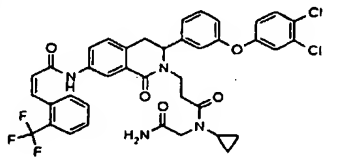
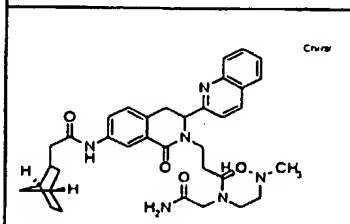
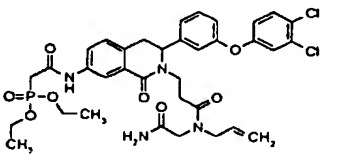
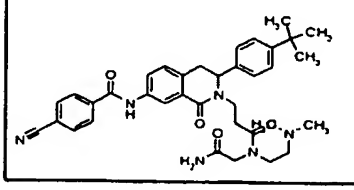
	$C_{36}H_{37}F_2N_5O_5$	657.7143	99.18
	$C_{33}H_{31}F_8N_5O_4$	713.6229	99.18
	$C_{36}H_{38}F_3N_5O_4$	661.7212	99.18
	$C_{37}H_{41}N_5O_5$	635.7609	99.17
	$C_{34}H_{35}F_6N_5O_4$	691.6695	99.17
	$C_{38}H_{42}N_6O_5$	662.7868	99.15
	$C_{43}H_{44}N_6O_5$	724.8576	99.15
	$C_{39}H_{31}F_5N_4O_6$	746.6859	99.15

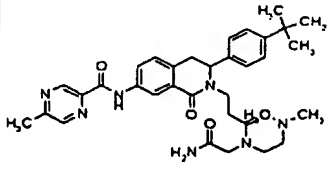
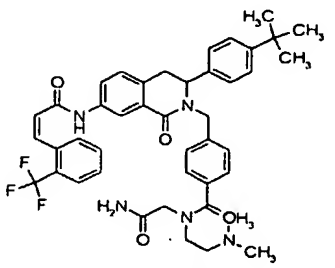
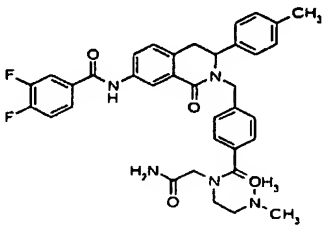
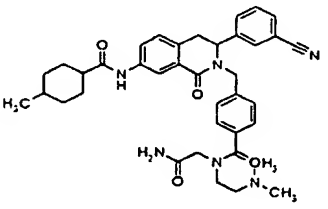
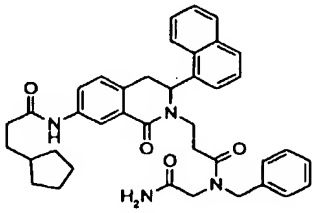
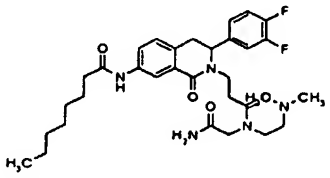
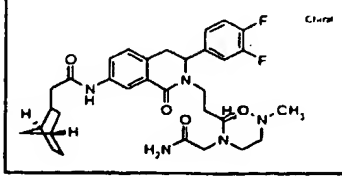
	$C_{44}H_{51}N_5O_5$	729.9169	99.15
	$C_{38}H_{44}F_3N_5O_4$	691.7906	99.03
	$C_{33}H_{35}N_7O_4$	593.6845	99.00
	$C_{38}H_{41}N_5O_4$	631.7729	99.00
	$C_{32}H_{35}N_7O_4S$	613.7395	99.00
	$C_{40}H_{43}F_2N_5O_4$	695.8067	98.99

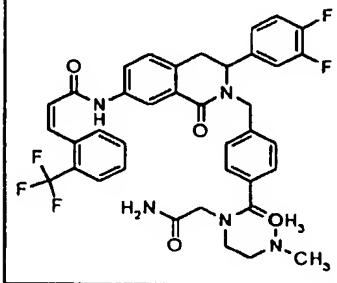
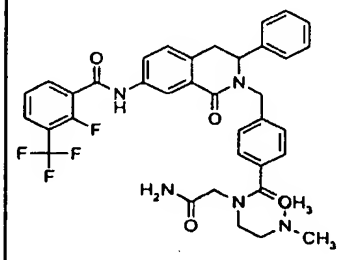
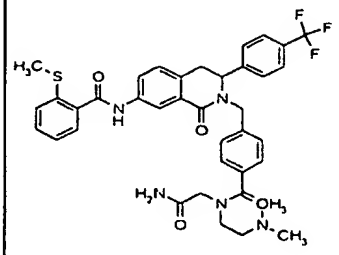
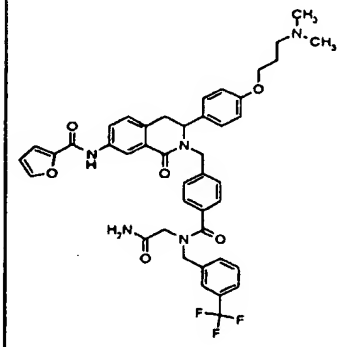
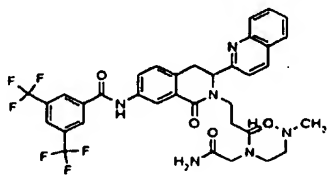
	$C_{35}H_{51}N_5O_6$	637.8169	98.98
	$C_{38}H_{56}N_6O_5$	676.8974	98.97
	$C_{37}H_{54}N_6O_5$	662.8706	98.97
	$C_{31}H_{41}F_3N_5O_7P$	683.6609	98.93
	$C_{36}H_{40}F_3N_5O_5$	679.736	98.93
	$C_{35}H_{35}IN_6O_4$	730.5995	98.83

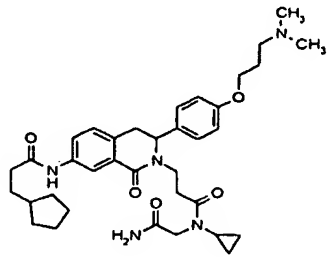
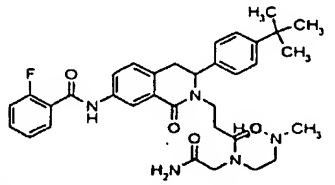
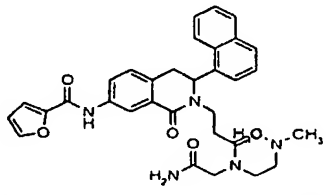
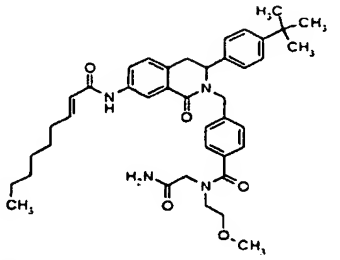
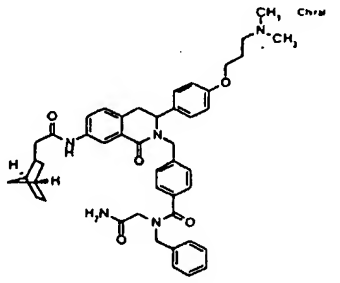
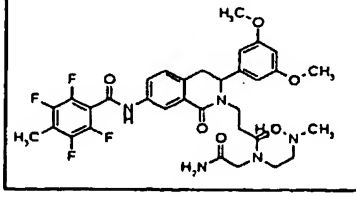
	$C_{36}H_{53}N_5O_5$	635.8447	98.83
	$C_{40}H_{41}F_3IN_5O_5$	855.6879	98.82
	$C_{48}H_{48}F_3N_5O_5$	831.9312	98.82
	$C_{36}H_{37}ClN_6O_4$	653.1793	98.81
	$C_{42}H_{55}N_5O_6$	725.9255	98.79
	$C_{42}H_{53}N_5O_6$	723.9097	98.79

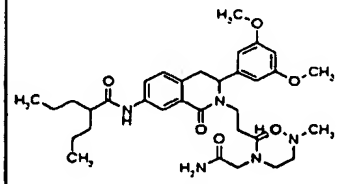
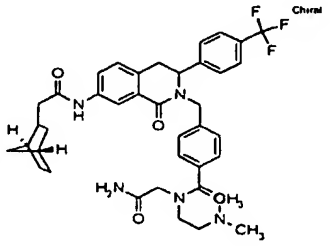
	$C_{39}H_{48}F_3N_5O_4$	707.8332	98.73
	$C_{35}H_{41}F_2N_5O_4$	633.7359	98.73
	$C_{42}H_{41}Cl_2F_3N_4O_5$	809.7089	98.70
	$C_{39}H_{47}N_5O_6$	681.8293	98.69
	$C_{35}H_{33}F_6N_7O_4$	729.6787	98.67
	$C_{40}H_{46}N_6O_4$	674.8414	98.59

	$C_{37}H_{54}N_6O_5$	662.8706	98.58
	$C_{46}H_{52}N_6O_6$	784.9528	98.58
	$C_{41}H_{52}F_3N_5O_5$	751.8858	98.55
	$C_{39}H_{33}Cl_2F_3N_4O_5$	765.6127	98.55
	$C_{36}H_{44}N_6O_4$	624.7816	98.53
	$C_{35}H_{39}Cl_2N_4O_8P$	745.5931	98.51
	$C_{36}H_{42}N_6O_4$	622.7658	98.47

	$C_{34}H_{43}N_7O_4$	613.7587	98.47
	$C_{43}H_{46}F_3N_5O_4$	753.8614	98.47
	$C_{37}H_{37}F_2N_5O_4$	653.7263	98.46
	$C_{38}H_{44}N_6O_4$	648.8036	98.45
	$C_{39}H_{42}N_4O_4$	630.7848	98.43
	$C_{32}H_{43}F_2N_5O_4$	599.7187	98.36
	$C_{33}H_{41}F_2N_5O_4$	609.7139	98.36

	$C_{39}H_{36}F_5N_5O_4$	733.7344	98.36
	$C_{37}H_{35}F_4N_5O_4$	689.7065	98.35
	$C_{38}H_{38}F_3N_5O_4S$	717.8092	98.30
	$C_{43}H_{42}F_3N_5O_6$	781.8278	98.29
	$C_{36}H_{34}F_6N_6O_4$	728.6906	98.22

	$C_{36}H_{49}N_5O_5$	631.8131	98.21
	$C_{35}H_{42}FN_5O_4$	615.7458	98.20
	$C_{33}H_{35}N_5O_5$	581.6695	98.20
	$C_{41}H_{52}N_4O_5$	680.8848	98.17
	$C_{46}H_{53}N_5O_5$	755.9547	98.17
	$C_{34}H_{37}F_4N_5O_6$	687.6873	98.16

	$C_{34}H_{49}N_5O_6$	623.7901	98.16
	$C_{39}H_{44}F_3N_5O_4$	703.8016	98.14

EXAMPLE 17

Penile Erection Due to Administration of DHQ Compound

Adult male rats are housed 2-3 per cage and are acclimated to the standard vivarium light cycle (12 hr. light, 12 hr. dark), rat chow and water for a least a week prior to testing. All experiments are performed between 9 a.m. and noon and rats are placed in cylindrical, clear plexiglass chambers during the 60 minute observation period. Mirrors are positioned below and to the sides of the chambers, to improve viewing.

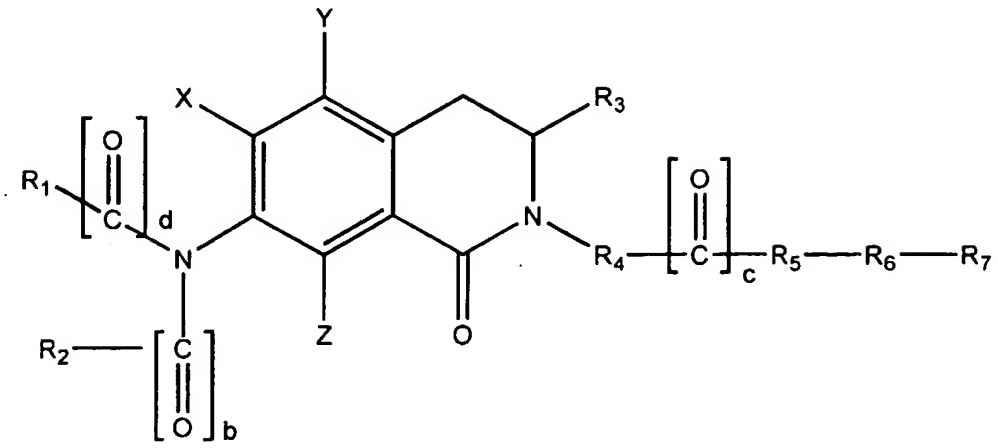
Observations begin 10 minutes after an unstraperitoneal injection of either saline or compound. An observer counts the number of grooming motions, stretches, yawns and penile erections (spontaneously occurring, not elicited by genital grooming) and records them every 5 minutes, for a total of 60 minutes. The observer is unaware of the treatment and animals are tested once, with n=6 in each group. Values in the figures represent the group mean and standard error of the mean. HP 228 can be used as a positive control for penile erections. Significant differences between groups are determined by an overall analysis of variance and the Student Neunmann-Keuls post hoc test can be used to identify individual differences between groups ($p \leq 0.05$).

Although the invention has been described with reference to the examples provided above, it should be understood that various modifications can be made by those skilled in the art without departing from the

invention. Accordingly, the invention is set out in the following claims.

WE CLAIM:

1. A combinatorial library of two or more compounds of the formula:



wherein:

R_1 and R_2 are, independently, selected from the group consisting of a hydrogen atom, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, C_2 to C_{12} alkenyl, C_2 to C_{12} substituted alkenyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, C_1 to C_{12} heterocyclicalkyl, C_1 to C_{12} substituted heterocyclicalkyl, heteroaryl, substituted heteroaryl, heterocycle and substituted heterocycle;

R_3 is selected from the group consisting of a hydrogen atom, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, phenyl, substituted phenyl, heteroaryl, substituted heteroaryl, carboxy, protected carboxy, cyano, protected (monosubstituted)amino, (disubstituted)amino, C_1 to C_{12} acyl, C_1 to C_{12} substituted acyl, C_1 to C_{12} alkoxycarbonyl, C_1 to C_{12} substituted alkoxycarbonyl, C_1 to C_{12} alkylaminocarbonyl, C_1 to C_{12} substituted

alkylaminocarbonyl, phenylaminocarbonyl, substituted phenylaminocarbonyl, heterocycle, substituted heterocycle, naphthyl, substituted naphthyl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl and C_5 to C_7 substituted cycloalkenyl;

R_4 is absent or is selected from the group consisting of the formula:

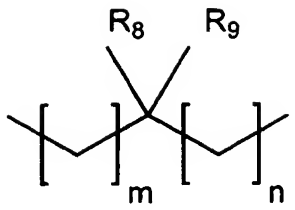
-D-W-E-

wherein:

W is absent or selected from the group consisting of C_3 to C_7 cycloalkylene, C_3 to C_7 substituted cycloalkylene, C_5 to C_7 cycloalkenylene, C_5 to C_7 substituted cycloalkenylene, arylene, substituted arylene, heterocyclene, substituted heterocyclene, heteroarylene and substituted heteroarylene;

and D, which is directly attached to the nitrogen depicted in the formula, and E are independently absent or independently selected from the group consisting of C_1 to C_{12} alkylene, C_2 to C_{12} alkenylene, C_2 to C_{12} alkynylene, C_1 to C_{12} substituted alkylene, C_2 to C_{12} substituted alkenylene, C_2 to C_{12} substituted alkynylene, C_3 to C_7 cycloalkylene, C_3 to C_7 substituted cycloalkylene, C_5 to C_7 cycloalkenylene, C_5 to C_7 substituted cycloalkenylene, C_7 to C_{18} phenylalkylene, C_7 to C_{18} substituted phenylalkylene, C_1 to C_{12} heterocyclicalkylene and C_1 to C_{12} substituted heterocyclicalkylene;

and the formula:



wherein:

R_8 and R_9 are together or independently selected from the group consisting of a hydrogen atom, C_1 to C_{12} alkyl, C_2 to C_{12} alkenyl, C_2 to C_{12} alkynyl, C_1 to C_{12} substituted alkyl, C_2 to C_{12} substituted alkenyl, C_2 to C_{12} substituted alkynyl, C_1 to C_{12} acyl, C_1 to C_{12} substituted acyl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl, C_5 to C_7 substituted cycloalkenyl, a heterocyclic ring, substituted heterocyclic ring, heteroaryl, substituted heteroaryl, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, C_1 to C_{12} heterocyclicalkyl, C_1 to C_{12} substituted heterocyclicalkyl, C_7 to C_{18} phenylalkoxy, C_7 to C_{18} substituted phenylalkoxy, phenyl, substituted phenyl, naphthyl, substituted naphthyl, cyclic C_2 to C_7 alkylene, substituted cyclic C_2 to C_7 alkylene, cyclic C_2 to C_7 heteroalkylene, substituted cyclic C_2 to C_7 heteroalkylene, carboxy, protected carboxy, hydroxymethyl, protected hydroxymethyl, amino and amino-protecting group; and m and n are independently 0, 1, 2, 3 or 4;

R_5 is absent or selected from the group consisting of -O-, -S-, amino, (monosubstituted)amino, protected (monosubstituted)amino,

the formula -D-W-E- as defined herein,

the formula K-L-M, wherein K and M are, independently, selected from the group consisting of amino, (monosubstituted)amino and protected (monosubstituted)amino, and L is absent or selected from the group consisting of C_1 to C_{12} alkylene, C_1 to C_{12} substituted alkylene, C_2 to C_{12} alkenylene, C_2 to C_{12} substituted alkenylene, C_3 to C_7 cycloalkylene, C_3 to C_7 substituted cycloalkylene, C_5 to C_7 cycloalkenylene, C_5 to C_7 substituted cycloalkenylene, arylene, substituted arylene, heterocyclene, substituted heterocyclene, heteroarylene and substituted heteroarylene, and

the formula $-NR_{12}-$ wherein R_{12} is selected from a hydrogen atom, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, C_1 to C_{12} heterocyclicalkyl, C_1 to C_{12} substituted heterocyclicalkyl, C_7 to C_{18} phenylalkoxy, C_7 to C_{18} substituted phenylalkoxy C_1 to C_{12} acyl, C_1 to C_{12} substituted acyl, phenylsulfonyl, substituted phenylsulfonyl, C_1 to C_{10} alkylsulfonyl, C_1 to C_{10} substituted alkylsulfonyl, C_1 to C_{12} alkylaminocarbonyl, C_1 to C_{12} substituted alkylaminocarbonyl, phenylaminocarbonyl, substituted phenylaminocarbonyl, C_1 to C_{12}

alkylaminothiocarbonyl, C_1 to C_{12} substituted alkylaminothiocarbonyl, phenylaminothiocarbonyl, substituted phenylaminothiocarbonyl, amino, (monosubstituted)amino, (disubstituted)amino, protected (monosubstituted)amino, C_1 to C_{12} alkylamino, C_1 to C_{12} alkyl(monosubstituted)amino, C_1 to C_{12} alkyl(disubstituted)amino, C_1 to C_{12} alkyl protected (monosubstituted)amino, C_1 to C_{12} substituted alkylamino, C_1 to C_{12} substituted alkyl(monosubstituted)amino, C_1 to C_{12} substituted alkyl(disubstituted)amino and C_1 to C_{12} substituted alkyl protected (monosubstituted)amino;

R_6 is absent or selected from the group consisting of C_1 to C_{12} alkylene, C_1 to C_{12} substituted alkylene, C_2 to C_{12} alkenylene and C_2 to C_{12} substituted alkenylene; and

R_7 is selected from the group consisting of a hydrogen atom, a halide, $-OR_{13}$, $-CO_2R_{13}$, $-C(O)NR_{13}R_{14}$ and $-NR_{13}R_{14}$, wherein R_{13} and R_{14} are independently selected from a functionalized resin, a hydrogen atom, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, phenyl, substituted phenyl, heterocycle, substituted heterocycle, heteroaryl, substituted heteroaryl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl, C_5 to C_7 substituted cycloalkenyl, C_7 to C_{18} phenylalkyl, C_7 to C_{12} substituted phenylalkyl, C_1 to C_{12} heterocyclicalkyl, C_1 to C_{12} substituted heterocyclicalkyl, C_1 to C_{12} acyl, C_1 to C_{12} substituted acyl, phenylsulfonyl, substituted phenylsulfonyl, C_1 to C_{10} alkylsulfonyl, C_1 to C_{10} substituted alkylsulfonyl, C_1 to C_{12} alkylaminocarbonyl, C_1 to C_{12} substituted alkylaminocarbonyl, phenylaminocarbonyl, substituted phenylaminocarbonyl, C_1

to C_{12} alkylaminothiocarbonyl, C_1 to C_{12} substituted alkylaminothiocarbonyl, phenylaminothiocarbonyl and substituted phenylaminothiocarbonyl;

X, Y and Z are, independently, selected from the group consisting of a hydrogen atom, halo, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_{12} alkyl, C_2 to C_{12} alkenyl, C_2 to C_{12} alkynyl, C_1 to C_{12} substituted alkyl, C_2 to C_{12} substituted alkenyl, C_2 to C_{12} substituted alkynyl, C_1 to C_{12} alkoxy, C_1 to C_{12} substituted alkoxy, C_1 to C_{12} acyloxy, C_1 to C_{12} acyl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl, C_5 to C_7 substituted cycloalkenyl, heterocyclic ring, substituted heterocyclic ring, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, C_1 to C_{12} heterocyclicalkyl, C_1 to C_{12} substituted heterocyclicalkyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, cyclic C_2 to C_7 alkylene, substituted cyclic C_2 to C_7 alkylene, cyclic C_2 to C_7 heteroalkylene, substituted cyclic C_2 to C_7 heteroalkylene, carboxy, protected carboxy, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, C_1 to C_{10} alkylthio, C_1 to C_{10} substituted alkylthio, C_1 to C_{10} alkylsulfonyl, C_1 to C_{10} substituted alkylsulfonyl, C_1 to C_{10} alkylsulfoxide, C_1 to C_{10} substituted alkylsulfoxide, phenylthio, substituted phenylthio, phenylsulfoxide, substituted phenylsulfoxide, phenylsulfonyl and substituted phenylsulfonyl; and

b, c and d are, independently, 0 or 1 and, when 0, the absent carbonyl can be replaced with $-SO_2-$; or

a pharmaceutically acceptable salt of a compound thereof.

2. The combinatorial library of claim 1, wherein R_1 is a hydrogen atom, b is 1, d is 0 and R_2 is selected from the group consisting of C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, C_2 to C_{12} alkenyl, C_2 to C_{12} substituted alkenyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, C_1 to C_{12} heterocyclicalkyl, C_1 to C_{12} substituted heterocyclicalkyl, heteroaryl, substituted heteroaryl, heterocycle and substituted heterocycle.

3. The combinatorial library of claim 1, wherein R_3 is selected from the group consisting of phenyl, substituted phenyl, heteroaryl, substituted heteroaryl, heterocycle, substituted heterocycle, naphthyl and substituted naphthyl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl and C_5 to C_7 substituted cycloalkenyl.

4. The combinatorial library of claim 1, wherein R_4 is the formula:

-D-W-E-

wherein:

W is absent or selected from the group consisting of arylene and substituted arylene; and

D and E are independently absent or independently selected from the group consisting of C_1 to C_{12} alkylene and C_1 to C_{12} substituted alkylene.

5. The combinatorial library of claim 1, wherein c is 1.

6. The combinatorial library of claim 1, wherein R_5 is absent or selected from the group consisting of -O-; the formula -D-W-E- wherein W is selected from the group consisting of heterocyclene and substituted heterocyclene and D and E are independently absent or independently selected from the group consisting of C_1 to C_{12} alkylene and C_1 to C_{12} substituted alkylene; and the formula $-NR_{12}-$, wherein R_{12} is selected from a hydrogen atom, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, C_1 to C_{12} heterocyclicalkyl, C_1 to C_{12} substituted heterocyclicalkyl, C_7 to C_{18} phenylalkoxy, C_7 to C_{18} substituted phenylalkoxy, C_1 to C_{12} acyl, C_1 to C_{12} substituted acyl, phenylsulfonyl, substituted phenylsulfonyl, C_1 to C_{10} alkylsulfonyl, C_1 to C_{10} substituted alkylsulfonyl, C_1 to C_{12} alkylaminocarbonyl, C_1 to C_{12} substituted alkylaminocarbonyl, phenylaminocarbonyl, substituted phenylaminocarbonyl, C_1 to C_{12} alkylaminothiocarbonyl, C_1 to C_{12} substituted alkylaminothiocarbonyl, phenylaminothiocarbonyl, substituted phenylaminothiocarbonyl, amino, (monosubstituted)amino, (disubstituted)amino, protected (monosubstituted)amino, C_1 to C_{12} alkylamino, C_1 to C_{12} alkyl(monosubstituted)amino, C_1 to C_{12} alkyl(disubstituted)amino, C_1 to C_{12} alkyl protected (monosubstituted)amino, C_1 to C_{12} substituted alkylamino, C_1 to C_{12} substituted alkyl(monosubstituted)amino, C_1 to C_{12} substituted alkyl(disubstituted)amino and C_1 to C_{12} substituted alkyl protected (monosubstituted)amino.

7. The combinatorial library of claim 1, wherein R_6 is C_1 to C_{12} alkylene.

8. The combinatorial library of claim 1, wherein R_7 is $-C(O)NR_{13}R_{14}$, wherein R_{13} and R_{14} are independently selected from a functionalized resin, a hydrogen atom, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, phenyl, substituted phenyl, heterocycle, substituted heterocycle, heteroaryl, substituted heteroaryl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl, C_5 to C_7 substituted cycloalkenyl, C_7 to C_{18} phenylalkyl, C_7 to C_{12} substituted phenylalkyl, C_1 to C_{12} heterocyclicalkyl, C_1 to C_{12} substituted heterocyclicalkyl, C_1 to C_{12} acyl, C_1 to C_{12} substituted acyl, phenylsulfonyl, substituted phenylsulfonyl, C_1 to C_{10} alkylsulfonyl, C_1 to C_{10} substituted alkylsulfonyl, C_1 to C_{12} alkylaminocarbonyl, C_1 to C_{12} substituted alkylaminocarbonyl, phenylaminocarbonyl, substituted phenylaminocarbonyl, C_1 to C_{12} alkylaminothiocarbonyl, C_1 to C_{12} substituted alkylaminothiocarbonyl, phenylaminothiocarbonyl and substituted phenylaminothiocarbonyl.

9. The combinatorial library of claim 1, wherein X, Y and Z are each a hydrogen atom.

10. The combinatorial library of claim 1, wherein:

R_1 is a hydrogen atom, b is 1, d is 0 and R_2 is selected from the group consisting of C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, C_2 to C_{12} alkenyl, C_2 to C_{12} substituted alkenyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, C_1 to C_{12} heterocyclicalkyl, C_1 to C_{12} substituted heterocyclicalkyl, heteroaryl, substituted heteroaryl, heterocycle and substituted heterocycle;

R_3 is selected from the group consisting of phenyl, substituted phenyl, heteroaryl, substituted heteroaryl, heterocycle, substituted heterocycle, naphthyl and substituted naphthyl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl and C_5 to C_7 substituted cycloalkenyl;

R_4 is the formula:

-D-W-E-

wherein:

W is absent or selected from the group consisting of arylene and substituted arylene; and

D, if present, is directly attached to the isoquinoline ring and D and E are independently absent or independently selected from the group consisting of C_1 to C_{12} alkylene and C_1 to C_{12} substituted alkylene;

c is 1;

R_5 is absent or selected from the group consisting of -O-; the formula -D-W-E- wherein W is selected from the group consisting of heterocyclene and substituted heterocyclene and D and E are independently absent or independently selected from the group consisting of C_1 to C_{12} alkylene and C_1 to C_{12} substituted alkylene; and the formula $-NR_{12}-$, wherein R_{12} is selected from a hydrogen atom, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, C_1 to C_{12} heterocyclicalkyl, C_1 to C_{12} substituted heterocyclicalkyl, C_7 to C_{18} phenylalkoxy, C_7 to C_{18}

substituted phenylalkoxy, C_1 to C_{12} acyl, C_1 to C_{12} substituted acyl, phenylsulfonyl, substituted phenylsulfonyl, C_1 to C_{10} alkylsulfonyl, C_1 to C_{10} substituted alkylsulfonyl, C_1 to C_{12} alkylaminocarbonyl, C_1 to C_{12} substituted alkylaminocarbonyl, phenylaminocarbonyl, substituted phenylaminocarbonyl, C_1 to C_{12} alkylaminothiocarbonyl, C_1 to C_{12} substituted alkylaminothiocarbonyl, phenylaminothiocarbonyl, substituted phenylaminothiocarbonyl, amino, (monosubstituted)amino, (disubstituted)amino, protected (monosubstituted)amino, C_1 to C_{12} alkylamino, C_1 to C_{12} alkyl(monosubstituted)amino, C_1 to C_{12} alkyl(disubstituted)amino, C_1 to C_{12} alkyl protected (monosubstituted)amino, C_1 to C_{12} substituted alkylamino, C_1 to C_{12} substituted alkyl(monosubstituted)amino, C_1 to C_{12} substituted alkyl(disubstituted)amino and C_1 to C_{12} substituted alkyl protected (monosubstituted)amino;

R_6 is C_1 to C_{12} alkylene;

R_7 is $-C(O)NR_{13}R_{14}$, wherein R_{13} and R_{14} are independently selected from a functionalized resin, a hydrogen atom, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, phenyl, substituted phenyl, heterocycle, substituted heterocycle, heteroaryl, substituted heteroaryl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl, C_5 to C_7 substituted cycloalkenyl, C_7 to C_{18} phenylalkyl, C_7 to C_{12} substituted phenylalkyl, C_1 to C_{12} heterocyclicalkyl, C_1 to C_{12} substituted heterocyclicalkyl, C_1 to C_{12} acyl, C_1 to C_{12} substituted acyl, phenylsulfonyl, substituted phenylsulfonyl, C_1 to C_{10} alkylsulfonyl, C_1 to C_{10} substituted alkylsulfonyl, C_1 to C_{12} alkylaminocarbonyl, C_1 to C_{12} substituted alkylaminocarbonyl, phenylaminocarbonyl, substituted phenylaminocarbonyl, C_1 to C_{12} alkylaminothiocarbonyl, C_1 to C_{12} substituted alkylaminothiocarbonyl,

phenylaminothiocarbonyl and substituted phenylaminothiocarbonyl; and

X, Y and Z are each a hydrogen atom.

11. The combinatorial library of claim 1, wherein

R_1 is a hydrogen atom, b is 1, d is 0 and R_2 is selected from the group consisting of 4-(trifluoromethoxy)phenyl, 2,6-difluorophenyl, 2-pyrazinyl, 2-furyl, 2,3,5,6-tetrafluoro-p-toluenyl, 3,4-difluorophenyl, (4-formylphenoxy)methyl, 2-(2-(trifluoromethyl))vinyl, (diethylphosphonyl)methyl, 2-fluoro-3-(trifluoromethyl)phenyl, 2-fluorophenyl, 4-cyanophenyl, (4-acetylphenoxy)methyl, 1-(phenyl)cyclopropyl, (3-phthalyl)methyl, mesitylformyl, 2-(6-methylchromyl), (2-naphthoxy)methyl, 3,5-bis(trifluoromethyl)phenyl, 3-(2-chloropyridyl), 2-(ethoxycarbonyl)vinyl, 5-(2-methylpyrazyl), 2-bromo-5-methoxyphenyl, 4-iodophenyl, 2-bromophenyl, 5-(4-methyl-1,2,3-thiadiazolyl), 2-(3,4,5-trimethoxyphenyl)vinyl, 2-(methylthio)phenyl, 3-(trifluoromethyl)benzyl, 2-methylcyclopropyl, 2-pentyl, methoxymethyl, 4-heptyl, 3,5,5-trimethylpentyl, allyl, 2-cyclopentylethyl, pentyl, 2-(tetrahydrofuryl), octyl, 2-cyclohexylethyl, heptyl, 3-methoxycyclohexyl, 4-methylcyclohexyl, 2-methylthioethyl, 2-methoxyethyl, (cyclopentyl)methyl, 2-methylnorbornyl and (methylthio)methyl;

R_3 is selected from the group consisting of phenyl, 1-naphthyl, 3-cyanophenyl, 2-imidazolyl, 2-pyridyl, 3-pyridyl, 2-quinolyl, 4-methylphenyl, 4-(3-dimethylaminopropoxy)phenyl, 4-(methylthio)phenyl, 4-(trifluoromethyl)phenyl, 3,5-dimethoxyphenyl,

3,4-difluorophenyl, 4-tert-butylphenyl, 4-acetamidophenyl, 3-(3,4-dichlorophenoxy)phenyl, 2-fluoryl, 2-(4-dimethylaminophenyl)vinyl, 4-dimethylaminophenyl and 2-propyl;

R_4 is 1,2-ethylene;

c is 1;

R_5 is $-NR_{12}-$, wherein R_{12} is selected from the group consisting of 2-(piperidyl)ethyl, 3-(imidazoyl)propyl, 2,4-dichlorophenethyl, 2-(2-pyridyl)ethyl, (3-pyridyl)methyl, 3-(trifluoromethyl)phenyl, 3-ethoxypropyl, 2-(4-morpholyl)ethyl, N-acetylamino, allyl, phenylmethyl, cyclopropyl, carbomethyoxyamino, 2(N,N-dibutylamino)ethyl, 2(N,N-dimethylamino)ethyl, propyl, 2-(4-methoxyphenyl)ethyl, cyclohexylmethyl, 3-diethylaminopropyl, 4-methylpiprazyl, 3-methoxybenzyl, (2-(1-ethyl-pyrrolidyl))methyl and 2-methoxyethyl;

R_6 is methylene;

R_7 is $-C(O)NR_{13}R_{14}$, wherein R_{13} is selected from the group consisting of a functionalized resin and a hydrogen atom and R_{14} is a hydrogen atom; and

X, Y and Z are each a hydrogen atom.

12. The combinatorial library of claim 1, wherein

R_1 is a hydrogen atom, b is 1, d is 0 and R_2 is selected from the group consisting of 4-(trifluoromethoxy)phenyl, 2,6-difluorophenyl, 2-pyrazinyl, 2-furyl, 2,3,5,6-tetrafluoro-p-toluenyl, 3,4-difluorophenyl, (4-formylphenoxy)methyl,

2-(2-(trifluoromethyl))vinyl, (diethylphosphonyl)methyl, 2-fluoro-3-(trifluoromethyl)phenyl, 2-fluorophenyl, 4-cyanophenyl, (4-acetylphenoxy)methyl, 1-(phenyl)cyclopropyl, (3-phthalyl)methyl, mesitylformyl, 2-(6-methylchromyl), (2-naphthoxy)methyl, 3,5-bis(trifluoromethyl)phenyl, 3-(2-chloropyridyl), 2-(ethoxycarbonyl)vinyl, 5-(2-methylpyrazyl), 2-bromo-5-methoxyphenyl, 4-iodophenyl, 2-bromophenyl, 5-(4-methyl-1,2,3-thiadiazolyl), 2-(3,4,5-trimethoxyphenyl)vinyl, 2-(methylthio)phenyl, 3-(trifluoromethyl)benzyl, 2-methylcyclopropyl, 2-pentyl, methoxymethyl, 4-heptyl, 3,5,5-trimethylpentyl, allyl, 2-cyclopentylethyl, pentyl, 2-(tetrahydrofuryl), octyl, 2-cyclohexylethyl, heptyl, 3-methoxycyclohexyl, 4-methylcyclohexyl, 2-methylthioethyl, 2-methoxyethyl, (cyclopentyl)methyl, 2-methylnorbornyl and (methylthio)methyl;

R_3 is selected from the group consisting of phenyl, 1-naphthyl, 3-cyanophenyl, 2-imidazolyl, 2-pyridyl, 3-pyridyl, 2-quinolyl, 4-methylphenyl, 4-(3-dimethylaminopropoxy)phenyl, 4-(methylthio)phenyl, 4-(trifluoromethyl)phenyl, 3,5-dimethoxyphenyl, 3,4-difluorophenyl, 4-tert-butylphenyl, 4-acetamidophenyl, 3-(3,4-dichlorophenoxy)phenyl, 2-fluoryl, 2-(4-dimethylaminophenyl)vinyl, 4-dimethylaminophenyl and 2-propyl;

R_4 is the formula -D-W-E-, wherein D is methylene, W is phenylene and E is absent;

c is 1;

R_5 is $-NR_{12}-$, wherein R_{12} is selected from the group consisting of 2-(piperidyl)ethyl, 3-(imidazoyl)propyl, 2,4-dichlorophenethyl, 2-(2-pyridyl)ethyl,

(3-pyridyl)methyl, 3-(trifluoromethyl)phenyl, 3-ethoxypropyl, 2-(4-morpholyl)ethyl, N-acetylamino, allyl, phenylmethyl, cyclopropyl, carbomethyoxyamino, 2(N,N-dibutylamino)ethyl, 2(N,N-dimethylamino)ethyl, propyl, 2-(4-methoxyphenyl)ethyl, cyclohexylmethyl, 3-diethylaminopropyl, 4-methylpiprazyl, 3-methoxybenzyl, (2-(1-ethyl-pyrrolidyl))methyl and 2-methoxyethyl;

R_6 is methylene;

R_7 is $-C(O)NR_{13}R_{14}$, wherein R_{13} is selected from the group consisting of a functionalized resin and a hydrogen atom and R_{14} is a hydrogen atom; and

X, Y and Z are each a hydrogen atom.

13. The combinatorial library of claim 1, wherein

R_1 is a hydrogen atom, b is 1, d is 0 and R_2 is selected from the group consisting of 4-(trifluoromethoxy)phenyl, 2,6-difluorophenyl, 2-pyrazinyl, 2-furyl, 2,3,5,6-tetrafluoro-p-toluenyl, 3,4-difluorophenyl, (4-formylphenoxy)methyl, 2-(2-(trifluoromethyl))vinyl, (diethylphosphonyl)methyl, 2-fluoro-3-(trifluoromethyl)phenyl, 2-fluorophenyl, 4-cyanophenyl, (4-acetylphenoxy)methyl, 1-(phenyl)cyclopropyl, (3-phthalyl)methyl, mesitylformyl, 2-(6-methylchromyl), (2-naphthoxy)methyl, 3,5-bis(trifluoromethyl)phenyl, 3-(2-chloropyridyl), 2-(ethoxycarbonyl)vinyl, 5-(2-methylpyrazyl), 2-bromo-5-methoxyphenyl, 4-iodophenyl, 2-bromophenyl, 5-(4-methyl-1,2,3-thiadiazolyl), 2-(3,4,5-trimethoxyphenyl)vinyl, 2-(methylthio)phenyl, 3-(trifluoromethyl)benzyl, 2-methylcyclopropyl, 2-pentyl, methoxymethyl, 4-heptyl, 3,5,5-trimethylpentyl, allyl,

2-cyclopentylethyl, pentyl, 2-(tetrahydrofuryl), octyl, 2-cyclohexylethyl, heptyl, 3-methoxycyclohexyl, 4-methylcyclohexyl, 2-methylthioethyl, 2-methoxyethyl, (cyclopentyl)methyl, 2-methylnorbornyl and (methylthio)methyl;

R_3 is selected from the group consisting of phenyl, 1-naphthyl, 3-cyanophenyl, 2-imidazolyl, 2-pyridyl, 3-pyridyl, 2-quinolyl, 4-methylphenyl, 4-(3-dimethylaminopropoxy)phenyl, 4-(methylthio)phenyl, 4-(trifluoromethyl)phenyl, 3,5-dimethoxyphenyl, 3,4-difluorophenyl, 4-tert-butylphenyl, 4-acetamidophenyl, 3-(3,4-dichlorophenoxy)phenyl, 2-fluoryl, 2-(4-dimethylaminophenyl)vinyl, 4-dimethylaminophenyl and 2-propyl;

R_4 is selected from the group consisting of 1,2-ethylene and the formula -D-W-E-, wherein D is methylene, W is phenylene and E is absent;

c is 1;

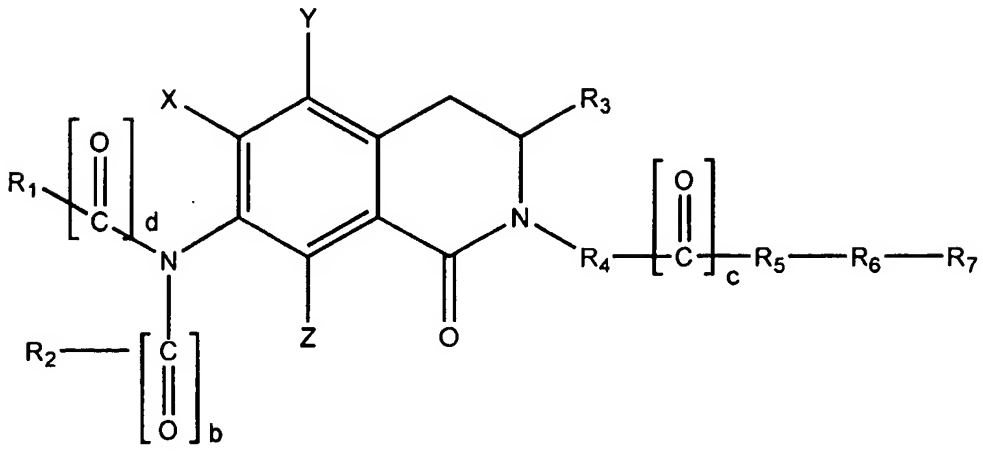
R_5 is selected from the group consisting of -O- and 1,4-piperazylene;

R_6 is methylene;

R_7 is $-C(O)NR_{13}R_{14}$, wherein R_{13} is selected from the group consisting of a functionalized resin and a hydrogen atom and R_{14} is a hydrogen atom; and

X, Y and Z are each a hydrogen atom.

14. A single compound of the formula:



wherein:

R_1 and R_2 are, independently, selected from the group consisting of a hydrogen atom, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, C_2 to C_{12} alkenyl, C_2 to C_{12} substituted alkenyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, C_1 to C_{12} heterocyclicalkyl, C_1 to C_{12} substituted heterocyclicalkyl, heteroaryl, substituted heteroaryl, heterocycle and substituted heterocycle;

R_3 is selected from the group consisting of C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, phenyl, substituted phenyl, heteroaryl, substituted heteroaryl, carboxy, protected carboxy, cyano, protected (monosubstituted)amino, (disubstituted)amino, C_1 to C_{12} acyl, C_1 to C_{12} substituted acyl, C_1 to C_{12} alkoxycarbonyl, C_1 to C_{12} substituted alkoxycarbonyl, C_1 to C_{12} alkylaminocarbonyl, C_1 to C_{12} substituted alkylaminocarbonyl, phenylaminocarbonyl, substituted phenylaminocarbonyl, heterocycle, substituted heterocycle, naphthyl, substituted naphthyl, C_3 to C_7

cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl and C_5 to C_7 substituted cycloalkenyl;

R_4 is absent or is selected from the group consisting of the formula:

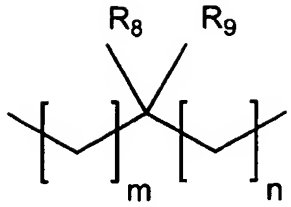
-D-W-E-

wherein:

W is absent or selected from the group consisting of C_3 to C_7 cycloalkylene, C_3 to C_7 substituted cycloalkylene, C_5 to C_7 cycloalkenylene, C_5 to C_7 substituted cycloalkenylene, arylene, substituted arylene, heterocyclene, substituted heterocyclene, heteroarylene and substituted heteroarylene;

and D, which is directly attached to the nitrogen depicted in the formula, and E are independently absent or independently selected from the group consisting of C_1 to C_{12} alkylene, C_2 to C_{12} alkenylene, C_2 to C_{12} alkynylene, C_1 to C_{12} substituted alkylene, C_2 to C_{12} substituted alkenylene, C_2 to C_{12} substituted alkynylene, C_3 to C_7 cycloalkylene, C_3 to C_7 substituted cycloalkylene, C_5 to C_7 cycloalkenylene, C_5 to C_7 substituted cycloalkenylene, C_7 to C_{18} phenylalkylene, C_7 to C_{18} substituted phenylalkylene, C_1 to C_{12} heterocyclicalkylene and C_1 to C_{12} substituted heterocyclicalkylene;

and the formula:



wherein:

R_8 and R_9 are together or independently selected from the group consisting of a hydrogen atom, C_1 to C_{12} alkyl, C_2 to C_{12} alkenyl, C_2 to C_{12} alkynyl, C_1 to C_{12} substituted alkyl, C_2 to C_{12} substituted alkenyl, C_2 to C_{12} substituted alkynyl, C_1 to C_{12} acyl, C_1 to C_{12} substituted acyl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl, C_5 to C_7 substituted cycloalkenyl, a heterocyclic ring, substituted heterocyclic ring, heteroaryl, substituted heteroaryl, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, C_1 to C_{12} heterocyclicalkyl, C_1 to C_{12} substituted heterocyclicalkyl, C_7 to C_{18} phenylalkoxy, C_7 to C_{18} substituted phenylalkoxy, phenyl, substituted phenyl, naphthyl, substituted naphthyl, cyclic C_2 to C_7 alkylene, substituted cyclic C_2 to C_7 alkylene, cyclic C_2 to C_7 heteroalkylene, substituted cyclic C_2 to C_7 heteroalkylene, carboxy, protected carboxy, hydroxymethyl, protected hydroxymethyl, amino and amino-protecting group; and m and n are independently 0, 1, 2, 3 or 4;

R_5 is absent or selected from the group consisting of -O-, -S-, amino, (monosubstituted)amino, protected (monosubstituted)amino,

the formula -D-W-E- as defined herein,

the formula K-L-M, wherein K and M are, independently, selected from the group consisting of amino, (monosubstituted)amino and protected (monosubstituted)amino, and L is absent or selected from the group consisting of C_1 to C_{12} alkylene, C_1 to C_{12} substituted alkylene, C_2 to C_{12} alkenylene, C_2 to C_{12} substituted alkenylene, C_3 to C_7 cycloalkylene, C_3 to C_7 substituted cycloalkylene, C_5 to C_7 cycloalkenylene, C_5 to C_7 substituted cycloalkenylene, arylene, substituted arylene, heterocyclene, substituted heterocyclene, heteroarylene and substituted heteroarylene, and

the formula $-NR_{12}-$, wherein R_{12} is selected from a hydrogen atom, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, C_1 to C_{12} heterocyclicalkyl, C_1 to C_{12} substituted heterocyclicalkyl, C_7 to C_{18} phenylalkoxy, C_7 to C_{18} substituted phenylalkoxy C_1 to C_{12} acyl, C_1 to C_{12} substituted acyl, phenylsulfonyl, substituted phenylsulfonyl, C_1 to C_{10} alkylsulfonyl, C_1 to C_{10} substituted alkylsulfonyl, C_1 to C_{12} alkylaminocarbonyl, C_1 to C_{12} substituted alkylaminocarbonyl, phenylaminocarbonyl, substituted phenylaminocarbonyl, C_1 to C_{12}

alkylaminothiocarbonyl, C_1 to C_{12} substituted alkylaminothiocarbonyl, phenylaminothiocarbonyl, substituted phenylaminothiocarbonyl, amino, (monosubstituted)amino, (disubstituted)amino, protected (monosubstituted)amino, C_1 to C_{12} alkylamino, C_1 to C_{12} alkyl(monosubstituted)amino, C_1 to C_{12} alkyl(disubstituted)amino, C_1 to C_{12} alkyl protected (monosubstituted)amino, C_1 to C_{12} substituted alkylamino, C_1 to C_{12} substituted alkyl(monosubstituted)amino, C_1 to C_{12} substituted alkyl(disubstituted)amino and C_1 to C_{12} substituted alkyl protected (monosubstituted)amino;

R_6 is absent or selected from the group consisting of C_1 to C_{12} alkylene, C_1 to C_{12} substituted alkylene, C_2 to C_{12} alkenylene and C_2 to C_{12} substituted alkenylene; and

R_7 is selected from the group consisting of a hydrogen atom, a halide, $-OR_{13}$, $-CO_2R_{13}$, $-C(O)NR_{13}R_{14}$ and $-NR_{13}R_{14}$, wherein R_{13} and R_{14} are independently selected from a hydrogen atom, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, phenyl, substituted phenyl, heterocycle, substituted heterocycle, heteroaryl, substituted heteroaryl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl, C_5 to C_7 substituted cycloalkenyl, C_7 to C_{18} phenylalkyl, C_7 to C_{12} substituted phenylalkyl, C_1 to C_{12} heterocyclicalkyl, C_1 to C_{12} substituted heterocyclicalkyl, C_1 to C_{12} acyl, C_1 to C_{12} substituted acyl, phenylsulfonyl, substituted phenylsulfonyl, C_1 to C_{10} alkylsulfonyl, C_1 to C_{10} substituted alkylsulfonyl, C_1 to C_{12} alkylaminocarbonyl, C_1 to C_{12} substituted alkylaminocarbonyl, phenylaminocarbonyl, substituted phenylaminocarbonyl, C_1

to C_{12} alkylaminothiocarbonyl, C_1 to C_{12} substituted alkylaminothiocarbonyl, phenylaminothiocarbonyl and substituted phenylaminothiocarbonyl;

X, Y and Z are, independently, selected from the group consisting of a hydrogen atom, halo, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_{12} alkyl, C_2 to C_{12} alkenyl, C_2 to C_{12} alkynyl, C_1 to C_{12} substituted alkyl, C_2 to C_{12} substituted alkenyl, C_2 to C_{12} substituted alkynyl, C_1 to C_{12} alkoxy, C_1 to C_{12} substituted alkoxy, C_1 to C_{12} acyloxy, C_1 to C_{12} acyl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl, C_5 to C_7 substituted cycloalkenyl, heterocyclic ring, substituted heterocyclic ring, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, C_1 to C_{12} heterocyclicalkyl, C_1 to C_{12} substituted heterocyclicalkyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, cyclic C_2 to C_7 alkylene, substituted cyclic C_2 to C_7 alkylene, cyclic C_2 to C_7 heteroalkylene, substituted cyclic C_2 to C_7 heteroalkylene, carboxy, protected carboxy, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, C_1 to C_{10} alkylthio, C_1 to C_{10} substituted alkylthio, C_1 to C_{10} alkylsulfonyl, C_1 to C_{10} substituted alkylsulfonyl, C_1 to C_{10} alkylsulfoxide, C_1 to C_{10} substituted alkylsulfoxide, phenylthio, substituted phenylthio, phenylsulfoxide, substituted phenylsulfoxide, phenylsulfonyl and substituted phenylsulfonyl;

b, c and d are, independently, 0 or 1 and, when 0, the absent carbonyl can be replaced with $-SO_2-$; or

a pharmaceutically acceptable salt of a compound thereof.

15. The single compound of claim 14, wherein R_1 is a hydrogen atom, b is 1, d is 0 and R_2 is selected from the group consisting of C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, C_2 to C_{12} alkenyl, C_2 to C_{12} substituted alkenyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, C_1 to C_{12} heterocyclicalkyl, C_1 to C_{12} substituted heterocyclicalkyl, heteroaryl, substituted heteroaryl, heterocycle and substituted heterocycle.

16. The single compound of claim 14, wherein R_3 is selected from the group consisting of phenyl, substituted phenyl, heteroaryl, substituted heteroaryl, heterocycle, substituted heterocycle, naphthyl and substituted naphthyl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl and C_5 to C_7 substituted cycloalkenyl.

17. The single compound of claim 14, wherein R_4 is the formula:

-D-W-E-

wherein:

W is absent or selected from the group consisting of arylene and substituted arylene; and

D, if present, is directly attached to the isoquinoline ring and D and E are independently absent or independently selected from the group

consisting of C_1 to C_{12} alkylene and C_1 to C_{12} substituted alkylene.

18. The single compound of claim 14, wherein c is 1.

19. The single compound of claim 14, wherein R_5 is absent or selected from the group consisting of -O-; the formula -D-W-E- wherein W is selected from the group consisting of heterocyclene and substituted heterocyclene and D and E are independently absent or independently selected from the group consisting of C_1 to C_{12} alkylene and C_1 to C_{12} substituted alkylene; and the formula $-NR_{12}-$, wherein R_{12} is selected from a hydrogen atom, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, C_1 to C_{12} heterocyclicalkyl, C_1 to C_{12} substituted heterocyclicalkyl, C_7 to C_{18} phenylalkoxy, C_7 to C_{18} substituted phenylalkoxy, C_1 to C_{12} acyl, C_1 to C_{12} substituted acyl, phenylsulfonyl, substituted phenylsulfonyl, C_1 to C_{10} alkylsulfonyl, C_1 to C_{10} substituted alkylsulfonyl, C_1 to C_{12} alkylaminocarbonyl, C_1 to C_{12} substituted alkylaminocarbonyl, phenylaminocarbonyl, substituted phenylaminocarbonyl, C_1 to C_{12} alkylaminothiocarbonyl, C_1 to C_{12} substituted alkylaminothiocarbonyl, phenylaminothiocarbonyl, substituted phenylaminothiocarbonyl, amino, (monosubstituted)amino, (disubstituted)amino, protected (monosubstituted)amino, C_1 to C_{12} alkylamino, C_1 to C_{12} alkyl(monosubstituted)amino, C_1 to C_{12} alkyl(disubstituted)amino, C_1 to C_{12} alkyl protected (monosubstituted)amino, C_1 to C_{12} substituted alkylamino, C_1 to C_{12} substituted alkyl(monosubstituted)amino, C_1 to C_{12} substituted alkyl(disubstituted)amino and C_1 to C_{12} substituted alkyl protected (monosubstituted)amino.

20. The single compound of claim 14, wherein R_6 is C_1 to C_{12} alkylene.

21. The single compound of claim 14, wherein R_7 is $-C(O)NR_{13}R_{14}$, wherein R_{13} and R_{14} are independently selected from a hydrogen atom, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, phenyl, substituted phenyl, heterocycle, substituted heterocycle, heteroaryl, substituted heteroaryl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl, C_5 to C_7 substituted cycloalkenyl, C_7 to C_{18} phenylalkyl, C_7 to C_{12} substituted phenylalkyl, C_1 to C_{12} heterocyclicalkyl, C_1 to C_{12} substituted heterocyclicalkyl, C_1 to C_{12} acyl, C_1 to C_{12} substituted acyl, phenylsulfonyl, substituted phenylsulfonyl, C_1 to C_{10} alkylsulfonyl, C_1 to C_{10} substituted alkylsulfonyl, C_1 to C_{12} alkylaminocarbonyl, C_1 to C_{12} substituted alkylaminocarbonyl, phenylaminocarbonyl, substituted phenylaminocarbonyl, C_1 to C_{12} alkylaminothiocarbonyl, C_1 to C_{12} substituted alkylaminothiocarbonyl, phenylaminothiocarbonyl and substituted phenylaminothiocarbonyl.

22. The single compound of claim 14, wherein X, Y and Z are each a hydrogen atom.

23. The single compound of claim 14, wherein

R_1 is a hydrogen atom, b is 1, d is 0 and R_2 is selected from the group consisting of C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, C_2 to C_{12} alkenyl, C_2 to C_{12} substituted alkenyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, C_1 to C_{12} heterocyclicalkyl, C_1 to C_{12} substituted heterocyclicalkyl, heteroaryl, substituted heteroaryl, heterocycle and substituted heterocycle;

R_3 is selected from the group consisting of phenyl, substituted phenyl, heteroaryl, substituted heteroaryl, heterocycle, substituted heterocycle, naphthyl and substituted naphthyl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl and C_5 to C_7 substituted cycloalkenyl;

R_4 is the formula:

-D-W-E-

wherein:

W is absent or selected from the group consisting of arylene and substituted arylene; and

D, if present, is directly attached to the isoquinoline ring and D and E are independently absent or independently selected from the group consisting of C_1 to C_{12} alkylene and C_1 to C_{12} substituted alkylene;

c is 1;

R_5 is absent or selected from the group consisting of -O-; the formula -D-W-E- wherein W is selected from the group consisting of heterocyclene and substituted heterocyclene and D and E are independently absent or independently selected from the group consisting of C_1 to C_{12} alkylene and C_1 to C_{12} substituted alkylene; and the formula $-NR_{12}-$, wherein R_{12} is selected from a hydrogen atom, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, C_1 to C_{12} heterocyclicalkyl, C_1 to C_{12} substituted heterocyclicalkyl, C_7 to C_{18} phenylalkoxy, C_7 to C_{18}

substituted phenylalkoxy, C_1 to C_{12} acyl, C_1 to C_{12} substituted acyl, phenylsulfonyl, substituted phenylsulfonyl, C_1 to C_{10} alkylsulfonyl, C_1 to C_{10} substituted alkylsulfonyl, C_1 to C_{12} alkylaminocarbonyl, C_1 to C_{12} substituted alkylaminocarbonyl, phenylaminocarbonyl, substituted phenylaminocarbonyl, C_1 to C_{12} alkylaminothiocarbonyl, C_1 to C_{12} substituted alkylaminothiocarbonyl, phenylaminothiocarbonyl, substituted phenylaminothiocarbonyl, amino, (monosubstituted)amino, (disubstituted)amino, protected (monosubstituted)amino, C_1 to C_{12} alkylamino, C_1 to C_{12} alkyl(monosubstituted)amino, C_1 to C_{12} alkyl(disubstituted)amino, C_1 to C_{12} alkyl protected (monosubstituted)amino, C_1 to C_{12} substituted alkylamino, C_1 to C_{12} substituted alkyl(monosubstituted)amino, C_1 to C_{12} substituted alkyl(disubstituted)amino and C_1 to C_{12} substituted alkyl protected (monosubstituted)amino;

R_6 is C_1 to C_{12} alkylene;

R_7 is $-C(O)NR_{13}R_{14}$, wherein R_{13} and R_{14} are independently selected from a hydrogen atom, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, phenyl, substituted phenyl, heterocycle, substituted heterocycle, heteroaryl, substituted heteroaryl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl, C_5 to C_7 substituted cycloalkenyl, C_7 to C_{18} phenylalkyl, C_7 to C_{12} substituted phenylalkyl, C_1 to C_{12} heterocyclicalkyl, C_1 to C_{12} substituted heterocyclicalkyl, C_1 to C_{12} acyl, C_1 to C_{12} substituted acyl, phenylsulfonyl, substituted phenylsulfonyl, C_1 to C_{10} alkylsulfonyl, C_1 to C_{10} substituted alkylsulfonyl, C_1 to C_{12} alkylaminocarbonyl, C_1 to C_{12} substituted alkylaminocarbonyl, phenylaminocarbonyl, substituted phenylaminocarbonyl, C_1 to C_{12} alkylaminothiocarbonyl, C_1 to C_{12} substituted

alkylaminothiocarbonyl, phenylaminothiocarbonyl and substituted phenylaminothiocarbonyl; and

X, Y and Z are each a hydrogen atom.

24. The single compound of claim 14, wherein

R_1 is a hydrogen atom, b is 1, d is 0 and R_2 is selected from the group consisting of 4-(trifluoromethoxy)phenyl, 2,6-difluorophenyl, 2-pyrazinyl, 2-furyl, 2,3,5,6-tetrafluoro-p-toluenyl, 3,4-difluorophenyl, (4-formylphenoxy)methyl, 2-(2-(trifluoromethyl))vinyl, (diethylphosphonyl)methyl, 2-fluoro-3-(trifluoromethyl)phenyl, 2-fluorophenyl, 4-cyanophenyl, (4-acetylphenoxy)methyl, 1-(phenyl)cyclopropyl, (3-phthalyl)methyl, mesitylformyl, 2-(6-methylchromyl), (2-naphthoxy)methyl, 3,5-bis(trifluoromethyl)phenyl, 3-(2-chloropyridyl), 2-(ethoxycarbonyl)vinyl, 5-(2-methylpyrazyl), 2-bromo-5-methoxyphenyl, 4-iodophenyl, 2-bromophenyl, 5-(4-methyl-1,2,3-thiadiazolyl), 2-(3,4,5-trimethoxyphenyl)vinyl, 2-(methylthio)phenyl, 3-(trifluoromethyl)benzyl, 2-methylcyclopropyl, 2-pentyl, methoxymethyl, 4-heptyl, 3,5,5-trimethylpentyl, allyl, 2-cyclopentylethyl, pentyl, 2-(tetrahydrofuryl), octyl, 2-cyclohexylethyl, heptyl, 3-methoxycyclohexyl, 4-methylcyclohexyl, 2-methylthioethyl, 2-methoxyethyl, (cyclopentyl)methyl, 2-methylnorbornyl and (methylthio)methyl;

R_3 is selected from the group consisting of phenyl, 1-naphthyl, 3-cyanophenyl, 2-imidazolyl, 2-pyridyl, 3-pyridyl, 2-quinolyl, 4-methylphenyl, 4-(3-dimethylaminopropoxy)phenyl, 4-(methylthio)phenyl, 4-(trifluoromethyl)phenyl, 3,5-dimethoxyphenyl, 3,4-difluorophenyl, 4-tert-butylphenyl,

4-acetamidophenyl, 3-(3,4-dichlorophenoxy)phenyl, 2-fluoryl, 2-(4-dimethylaminophenyl)vinyl, 4-dimethylaminophenyl and 2-propyl;

R_4 is 1,2-ethylene;

c is 1;

R_5 is $-NR_{12}-$, wherein R_{12} is selected from the group consisting of 2-(piperidyl)ethyl, 3-(imidazoyl)propyl, 2,4-dichlorophenethyl, 2-(2-pyridyl)ethyl, (3-pyridyl)methyl, 3-(trifluoromethyl)phenyl, 3-ethoxypropyl, 2-(4-morpholyl)ethyl, N-acetylamino, allyl, phenylmethyl, cyclopropyl, carbomethyoxyamino, 2(N,N-dibutylamino)ethyl, 2(N,N-dimethylamino)ethyl, propyl, 2-(4-methoxyphenyl)ethyl, cyclohexylmethyl, 3-diethylaminopropyl, 4-methylpiprazyl, 3-methoxybenzyl, (2-(1-ethyl-pyrrolidyl))methyl and 2-methoxyethyl;

R_6 is methylene;

R_7 is $-C(O)NH_2$; and

X, Y and Z are each a hydrogen atom.

25. The single compound of claim 14, wherein

R_1 is a hydrogen atom, b is 1, d is 0 and R_2 is selected from the group consisting of 4-(trifluoromethoxy)phenyl, 2,6-difluorophenyl, 2-pyrazinyl, 2-furyl, 2,3,5,6-tetrafluoro-p-toluenyl, 3,4-difluorophenyl, (4-formylphenoxy)methyl, 2-(2-(trifluoromethyl))vinyl, (diethylphosphonyl)methyl, 2-fluoro-3-(trifluoromethyl)phenyl, 2-fluorophenyl, 4-cyanophenyl, (4-acetylphenoxy)methyl, 1-(phenyl)cyclopropyl, (3-phthalyl)methyl, mesitylformyl,

2-(6-methylchromyl), (2-naphthoxy)methyl, 3,5-bis(trifluoromethyl)phenyl, 3-(2-chloropyridyl), 2-(ethoxycarbonyl)vinyl, 5-(2-methylpyrazyl), 2-bromo-5-methoxyphenyl, 4-iodophenyl, 2-bromophenyl, 5-(4-methyl-1,2,3-thiadiazolyl), 2-(3,4,5-trimethoxyphenyl)vinyl, 2-(methylthio)phenyl, 3-(trifluoromethyl)benzyl, 2-methylcyclopropyl, 2-pentyl, methoxymethyl, 4-heptyl, 3,5,5-trimethylpentyl, allyl, 2-cyclopentylethyl, pentyl, 2-(tetrahydrofuryl), octyl, 2-cyclohexylethyl, heptyl, 3-methoxycyclohexyl, 4-methylcyclohexyl, 2-methylthioethyl, 2-methoxyethyl, (cyclopentyl)methyl, 2-methylnorbornyl and (methylthio)methyl;

R_3 is selected from the group consisting of phenyl, 1-naphthyl, 3-cyanophenyl, 2-imidazolyl, 2-pyridyl, 3-pyridyl, 2-quinolyl, 4-methylphenyl, 4-(3-dimethylaminopropoxy)phenyl, 4-(methylthio)phenyl, 4-(trifluoromethyl)phenyl, 3,5-dimethoxyphenyl, 3,4-difluorophenyl, 4-tert-butylphenyl, 4-acetamidophenyl, 3-(3,4-dichlorophenoxy)phenyl, 2-fluoryl, 2-(4-dimethylaminophenyl)vinyl, 4-dimethylaminophenyl and 2-propyl;

R_4 is the formula -D-W-E-, wherein D is methylene, W is phenylene and E is absent;

c is 1;

R_5 is $-NR_{12}-$, wherein R_{12} is selected from the group consisting of 2-(piperidyl)ethyl, 3-(imidazoyl)propyl, 2,4-dichlorophenethyl, 2-(2-pyridyl)ethyl, (3-pyridyl)methyl, 3-(trifluoromethyl)phenyl, 3-ethoxypropyl, 2-(4-morpholyl)ethyl, N-acetylamino, allyl, phenylmethyl, cyclopropyl, carbomethyoxyamino, 2(N,N-dibutylamino)ethyl, 2(N,N-dimethylamino)ethyl,

propyl, 2-(4-methoxyphenyl)ethyl, cyclohexylmethyl, 3-diethylaminopropyl, 4-methylpiprazyl, 3-methoxybenzyl, (2-(1-ethyl-pyrrolidyl))methyl and 2-methoxyethyl;

R_6 is methylene;

R_7 is $-C(O)NH_2$; and

X, Y and Z are each a hydrogen atom.

26. The single compound of claim 14, wherein

R_1 is a hydrogen atom, b is 1, d is 0 and R_2 is selected from the group consisting of 4-(trifluoromethoxy)phenyl, 2,6-difluorophenyl, 2-pyrazinyl, 2-furyl, 2,3,5,6-tetrafluoro-p-toluenyl, 3,4-difluorophenyl, (4-formylphenoxy)methyl, 2-(2-(trifluoromethyl))vinyl, (diethylphosphonyl)methyl, 2-fluoro-3-(trifluoromethyl)phenyl, 2-fluorophenyl, 4-cyanophenyl, (4-acetylphenoxy)methyl, 1-(phenyl)cyclopropyl, (3-phthalyl)methyl, mesitylformyl, 2-(6-methylchromyl), (2-naphthoxy)methyl, 3,5-bis(trifluoromethyl)phenyl, 3-(2-chloropyridyl), 2-(ethoxycarbonyl)vinyl, 5-(2-methylpyrazyl), 2-bromo-5-methoxyphenyl, 4-iodophenyl, 2-bromophenyl, 5-(4-methyl-1,2,3-thiadiazolyl), 2-(3,4,5-trimethoxyphenyl)vinyl, 2-(methylthio)phenyl, 3-(trifluoromethyl)benzyl, 2-methylcyclopropyl, 2-pentyl, methoxymethyl, 4-heptyl, 3,5,5-trimethylpentyl, allyl, 2-cyclopentylethyl, pentyl, 2-(tetrahydrofuryl), octyl, 2-cyclohexylethyl, heptyl, 3-methoxycyclohexyl, 4-methylcyclohexyl, 2-methylthioethyl, 2-methoxyethyl, (cyclopentyl)methyl, 2-methylnorbornyl and (methylthio)methyl;

R_3 is selected from the group consisting of phenyl, 1-naphthyl, 3-cyanophenyl, 2-imidazolyl, 2-pyridyl, 3-pyridyl, 2-quinolyl, 4-methylphenyl, 4-(3-dimethylaminopropoxy)phenyl, 4-(methylthio)phenyl, 4-(trifluoromethyl)phenyl, 3,5-dimethoxyphenyl, 3,4-difluorophenyl, 4-tert-butylphenyl, 4-acetamidophenyl, 3-(3,4-dichlorophenoxy)phenyl, 2-fluoryl, 2-(4-dimethylaminophenyl)vinyl, 4-dimethylaminophenyl and 2-propyl;

R_4 is selected from the group consisting of 1,2-ethylene and the formula -D-W-E-, wherein D is methylene, W is phenylene and E is absent;

c is 1;

R_5 is selected from the group consisting of -O- and 1,4-piperazylene;

R_6 is methylene;

R_7 is $-C(O)NH_2$; and

X, Y and Z are each a hydrogen atom.

27. A method of preparing a DHQ derivative compound, comprising:

(a) coupling a first compound having a leaving group with a second compound of the formula selected from the group consisting of (I) HOOC-variable group-NH-amino protecting group, (ii) nucleophilic group-variable group-NH-amino protecting group and (iii) nucleophilic group-sulfonyl-variable group-NH-amino protecting group;

(b) reacting the compound resulting from step (a) with an aldehyde compound having a variable group; and

(c) reacting the compound resulting from step (b) with 4-nitrohomophthalic anhydride, optionally substituted at one or more position of the phenyl ring other than the 4-nitro position, resulting in a DHQ derivative compound.

28. The method of claim 27, wherein said first compound is attached to solid support.

29. The method of claim 27, wherein said leaving group of said first compound is a halide.

30. The method of claim 27, further comprising reacting said first compound with a protected amine compound having a variable group.

31. The method of claim 27, further comprising reducing the nitro group of said DHQ derivative compound.

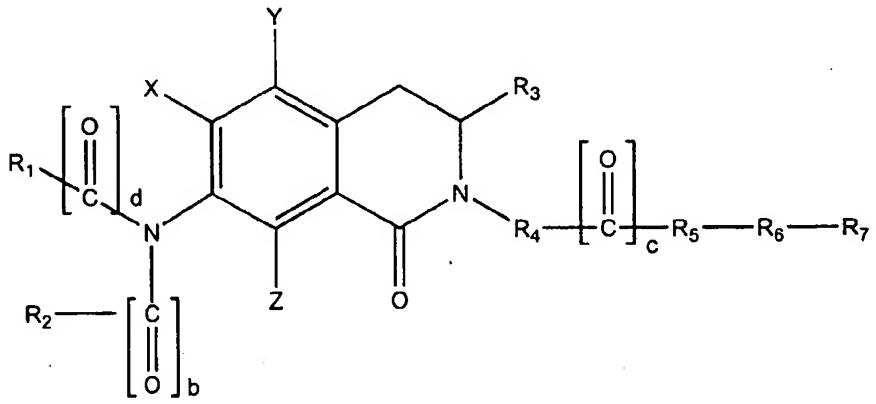
32. The method of claim 31, further comprising reacting said DHQ derivative with a compound selected from the group consisting of a carboxylic acid having a variable group, a halide having a variable group and a sulfonyl halide having a variable group.

33. The method of claim 30, further comprising reducing the nitro group of said DHQ derivative compound.

34. The method of claim 33, further comprising reacting said DHQ derivative compound with a compound selected from the group consisting of a carboxylic acid having a variable group, a halide having a variable group and a sulfonyl halide having a variable group.

AMENDED CLAIMS
[received by the International Bureau on 4 January 2001 (04.01.01);
new claim 35 added; remaining claims unchanged (7 pages)]

35. A single compound of the formula:



wherein:

R_1 and R_2 are, independently, selected from the group consisting of a hydrogen atom, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, C_2 to C_{12} alkenyl, C_2 to C_{12} substituted alkenyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, C_1 to C_{12} heterocyclicalkyl, C_1 to C_{12} substituted heterocyclicalkyl, heteroaryl, substituted heteroaryl, heterocycle and substituted heterocycle;

R_3 is selected from the group consisting of C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, phenyl, substituted phenyl, heteroaryl, substituted heteroaryl, carboxy, protected carboxy, cyano, protected (monosubstituted)amino, (disubstituted)amino, C_1 to C_{12} acyl, C_1 to C_{12} substituted acyl, C_1 to C_{12} alkoxycarbonyl, C_1 to C_{12} substituted alkoxycarbonyl, C_1 to C_{12} alkylaminocarbonyl, C_1 to C_{12} substituted alkylaminocarbonyl, phenylaminocarbonyl,

substituted phenylaminocarbonyl, heterocycle, substituted heterocycle, naphthyl, substituted naphthyl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl and C_5 to C_7 substituted cycloalkenyl;

R_4 is absent or is selected from the group consisting of the formula:

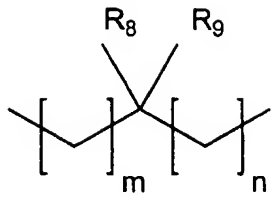
-D-W-E-

wherein:

W is absent or selected from the group consisting of C_3 to C_7 cycloalkylene, C_3 to C_7 substituted cycloalkylene, C_5 to C_7 cycloalkenylene, C_5 to C_7 substituted cycloalkenylene, arylene, substituted arylene, heterocyclene, substituted heterocyclene, heteroarylene and substituted heteroarylene;

and D, which is directly attached to the nitrogen depicted in the formula, and E are independently absent or independently selected from the group consisting of C_1 to C_{12} alkylene, C_2 to C_{12} alkenylene, C_2 to C_{12} alkynylene, C_1 to C_{12} substituted alkylene, C_2 to C_{12} substituted alkenylene, C_2 to C_{12} substituted alkynylene, C_3 to C_7 cycloalkylene, C_3 to C_7 substituted cycloalkylene, C_5 to C_7 cycloalkenylene, C_5 to C_7 substituted cycloalkenylene, C_7 to C_{18} phenylalkylene, C_7 to C_{18} substituted phenylalkylene, C_1 to C_{12} heterocyclicalkylene and C_1 to C_{12} substituted heterocyclicalkylene;

and the formula:



wherein:

R_8 and R_9 are together or independently selected from the group consisting of a hydrogen atom, C_1 to C_{12} alkyl, C_2 to C_{12} alkenyl, C_2 to C_{12} alkynyl, C_1 to C_{12} substituted alkyl, C_2 to C_{12} substituted alkenyl, C_2 to C_{12} substituted alkynyl, C_1 to C_{12} acyl, C_1 to C_{12} substituted acyl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl, C_5 to C_7 substituted cycloalkenyl, a heterocyclic ring, substituted heterocyclic ring, heteroaryl, substituted heteroaryl, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, C_1 to C_{12} heterocyclicalkyl, C_1 to C_{12} substituted heterocyclicalkyl, C_7 to C_{18} phenylalkoxy, C_7 to C_{18} substituted phenylalkoxy, phenyl, substituted phenyl, naphthyl, substituted naphthyl, cyclic C_2 to C_7 alkylene, substituted cyclic C_2 to C_7 alkylene, cyclic C_2 to C_7 heteroalkylene, substituted cyclic C_2 to C_7 heteroalkylene, carboxy, protected carboxy, hydroxymethyl, protected hydroxymethyl, amino

and amino-protecting group; and m and n are independently 0, 1, 2, 3 or 4;

R_5 is absent or selected from the group consisting of -O-, -S-, amino, (monosubstituted)amino, protected (monosubstituted)amino, the formula -D-W-E- as defined herein,

the formula K-L-M, wherein K and M are, independently, selected from the group consisting of amino, (monosubstituted)amino and protected (monosubstituted)amino, and L is absent or selected from the group consisting of C_1 to C_{12} alkylene, C_1 to C_{12} substituted alkylene, C_2 to C_{12} alkenylene, C_2 to C_{12} substituted alkenylene, C_3 to C_7 cycloalkylene, C_3 to C_7 substituted cycloalkylene, C_5 to C_7 cycloalkenylene, C_5 to C_7 substituted cycloalkenylene, arylene, substituted arylene, heterocyclene, substituted heterocyclene, heteroarylene and substituted heteroarylene, and

the formula $-NR_{12}-$, wherein R_{12} is selected from a hydrogen atom, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, C_1 to C_{12} heterocyclicalkyl, C_1 to C_{12} substituted heterocyclicalkyl, C_7 to C_{18} phenylalkoxy, C_7 to C_{18} substituted phenylalkoxy C_1 to C_{12} acyl, C_1 to C_{12} substituted acyl, phenylsulfonyl, substituted phenylsulfonyl, C_1 to C_{10}

alkylsulfonyl, C_1 to C_{10} substituted alkylsulfonyl, C_1 to C_{12} alkylaminocarbonyl, C_1 to C_{12} substituted alkylaminocarbonyl, phenylaminocarbonyl, substituted phenylaminocarbonyl, C_1 to C_{12} alkylaminothiocarbonyl, C_1 to C_{12} substituted alkylaminothiocarbonyl, phenylaminothiocarbonyl, substituted phenylaminothiocarbonyl, amino, (monosubstituted)amino, (disubstituted)amino, protected (monosubstituted)amino, C_1 to C_{12} alkylamino, C_1 to C_{12} alkyl(monosubstituted)amino, C_1 to C_{12} alkyl(disubstituted)amino, C_1 to C_{12} alkyl protected (monosubstituted)amino, C_1 to C_{12} substituted alkylamino, C_1 to C_{12} substituted alkyl(monosubstituted)amino, C_1 to C_{12} substituted alkyl(disubstituted)amino and C_1 to C_{12} substituted alkyl protected (monosubstituted)amino;

R_6 is absent or selected from the group consisting of C_1 to C_{12} alkylene, C_1 to C_{12} substituted alkylene, C_2 to C_{12} alkenylene and C_2 to C_{12} substituted alkenylene; and

R_7 is selected from the group consisting of $-C(O)NR_{13}R_{14}$ and $-NR_{13}R_{14}$, wherein R_{13} and R_{14} are independently selected from a hydrogen atom, C_1 to C_{12} alkyl, C_1 to C_{12} substituted alkyl, phenyl, substituted phenyl, heterocycle, substituted heterocycle, heteroaryl, substituted heteroaryl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl, C_5 to C_7 substituted cycloalkenyl, C_7 to C_{18} phenylalkyl, C_7 to C_{12} substituted phenylalkyl, C_1 to C_{12} heterocyclicalkyl, C_1 to C_{12} substituted heterocyclicalkyl, C_1 to C_{12} acyl, C_1 to C_{12} substituted acyl, phenylsulfonyl, substituted phenylsulfonyl, C_1 to C_{10} alkylsulfonyl, C_1 to C_{10} substituted alkylsulfonyl, C_1 to C_{12} alkylaminocarbonyl, C_1 to C_{12} substituted alkylaminocarbonyl, phenylaminocarbonyl, substituted phenylaminocarbonyl, C_1 to C_{12} alkylaminothiocarbonyl, C_1 to C_{12} substituted alkylaminothiocarbonyl, phenylaminothiocarbonyl and substituted phenylaminothiocarbonyl;

X, Y and Z are, independently, selected from the group consisting of a hydrogen atom, halo, hydroxy, protected hydroxy, cyano, nitro, C_1 to C_{12} alkyl, C_2 to C_{12} alkenyl, C_2 to C_{12} alkynyl, C_1 to C_{12} substituted alkyl, C_2 to C_{12} substituted alkenyl, C_2 to C_{12} substituted alkynyl, C_1 to C_{12} alkoxy, C_1 to C_{12} substituted alkoxy, C_1 to C_{12} acyloxy, C_1 tc C_{12} acyl, C_3 to C_7 cycloalkyl, C_3 to C_7 substituted cycloalkyl, C_5 to C_7 cycloalkenyl, C_5 to C_7 substituted cycloalkenyl, heterocyclic ring, substituted heterocyclic ring, C_7 to C_{18} phenylalkyl, C_7 to C_{18} substituted phenylalkyl, C_1 to C_{12} heterocyclicalkyl, C_1 to C_{12} substituted heterocyclicalkyl, phenyl, substituted phenyl, naphthyl, substituted naphthyl, cyclic C_2 to C_7 alkylene, substituted cyclic C_2 to C_7 alkylene, cyclic C_2 to C_7

heteroalkylene, substituted cyclic C_2 to C_7 heteroalkylene, carboxy, protected carboxy, hydroxymethyl, protected hydroxymethyl, amino, protected amino, (monosubstituted)amino, protected (monosubstituted)amino, (disubstituted)amino, carboxamide, protected carboxamide, C_1 to C_{10} alkylthio, C_1 to C_{10} substituted alkylthio, C_1 to C_{10} alkylsulfonyl, C_1 to C_{10} substituted alkylsulfonyl, C_1 to C_{10} alkylsulfoxide, C_1 to C_{10} substituted alkylsulfoxide, phenylthio, substituted phenylthio, phenylsulfoxide, substituted phenylsulfoxide, phenylsulfonyl and substituted phenylsulfonyl;

b, c and d are, independently, 0 or 1 and, when 0, the absent carbonyl can be replaced with $-SO_2-$; or

a pharmaceutically acceptable salt of a compound thereof.

STATEMENT UNDER ARTICLE 19

II. REMARKS

A. Regarding the Amendment.

New claim 35 has been added. The new claim is similar to original claim 14, except that R_7 is limited to specific formulae. The new claim is supported in the specification, for example, at page 10, lines 4-21, which recited these specific formulae.

Because the new claim is fully supported by the specification, no issue of new matter arises.

B. Regarding the ISR.

1. U.S. Pat. No. 5,602,145.

The International Search Report (ISR), mailed 8 November 2000, alleges that U.S. Pat. No. 5,602,145 (the '145 Patent) affects the novelty of claims 1, 2, 4 to 6, 9, 14, 15, 17 to 19 and 22. Further, the ISR alleges that the '145 Patent affects the inventiveness of claims 3, 7, 8, 10-13, 16, 20, 21, 23 and 24. The ISR specifically cites the Abstract, columns 1-7 and Examples 1-3 of the '145 Patent. (Applicant points out that WO 94/29273 A1, also cited in the ISR, is the same disclosure as the '145 Patent.)

a. Regarding the Abstract and columns 1-7 of the '145 Patent.

In response, Applicant points out that the Abstract and columns 1-7 of the '145 Patent are far too generic to render anything more specific (such as the subject claims) as lacking novelty or inventiveness. Specifically, the Abstract and columns 1-7 of the '145 Patent covers **any** bicyclic compound, substituted or unsubstituted, that has 0-2 ring nitrogens in the six-membered saturated ring and 0-2 heteroatoms (selected from any combination of O, S and N) in the unsaturated ring.

In view of the infinite array of bicyclic possibilities covered by the Abstract and columns 1-7 of the '145 Patent, the subject dihydroisoquinolinone (DHQ) compounds represent a **minute fraction** of the compounds encompassed by the generic description of the '145 patent. Accordingly, the generic disclosure of the Abstract and columns 1-7 of the '145 Patent provides no motivation for the skilled artisan to select any of the subject compounds. Therefore, this disclosure is insufficient to render the claims non-novel or non-inventive. See *Graham v. John Deere*, 383 U.S. 1 (1966), discussed fully in sec. 2144.08 of the M.P.E.P.

b. Regarding Examples 1-3 of the '145 Patent.

The ISR further cites Examples 1-3 of the '145 Patent. However, none of these compounds are within the scope of the claimed invention.

Specifically, Examples 1-3 each describes compounds that have hydrogen at the 3-position. By contrast, the corresponding position of the claimed invention, R_3, is required to be present (i.e., not hydrogen). Thus, neither the generic or specific

disclosure of the '145 Patent affects the novelty or inventiveness of any of the pending claims.

c. Regarding the combinatorial claims cited.

The ISR alleges the '145 patent affects the novelty of claims 1, 2, 4 to 6 and 9. However, all of these claims are directed to combinatorial libraries. By contrast, the '145 Patent is directed to serial (i.e., one-at-a-time) synthesis, and does not teach or suggest making or screening a library of compounds. Thus, in no way can the '145 Patent (either alone or in combination - see other references discussed below) affect the novelty (or even inventiveness) of any of the combinatorial library claims.

d. Regarding an alleged lack of inventiveness.

The ISR alleges that the '145 Patent affects the inventiveness of claims 16, 21, 23 and 24. However, each of these claims (as well as new claim 35) is so different from any compound exemplified in the '145 Patent that the inventiveness of these claims cannot be affected.

Specifically, claim 16 requires a cyclic moiety at the R_3 position. Similarly, species claim 24 requires a specific cyclic at the R_3 position. By contrast, as discussed above, the '145 Patent merely exemplifies compounds with hydrogen at the corresponding position. Thus, in no way would the skilled artisan be motivated to modify any compound taught in the '145 Patent to reach a compound within the scope of claims 16 or 24. Accordingly,

the '145 Patent does not affect the inventiveness of claims 16 or 24.

In addition, new claim 35 limits R_7 to a substituted carboxamide or a substituted amino. Similarly, claim 21 limits R_7 to a substituted carboxamide. By contrast, the '145 does not exemplify a compound that is remotely structurally similar to any encompassed by claim 35 or claim 21. Thus, in no way would the skilled artisan be motivated to modify any compound taught in the '145 Patent to reach a compound within the scope of claims 21 or 35. Accordingly, the '145 Patent does not affect the inventiveness of claims 21 or 35.

Finally, claim 23 requires both a cyclic moiety at the R_3 position and a substituted carboxamide at the R_7 position. By contrast, the '145 Patent does not exemplify a compound that is structurally similar at either of these positions, much less at both positions. Thus, in no way would the skilled artisan be motivated to modify any compound taught in the '145 Patent to reach a compound within the scope of claim 23. Accordingly, the '145 Patent does not affect the inventiveness of claim 23.

2. U.S. Pat. No. 5,629,321.

The ISR alleges that U.S. Pat. No. 5,629,321 (the '321 Patent) affects the novelty of claims 1, 2, 4 to 6, 9, 14, 15, 17 to 19 and 22. Further, the ISR alleges that the '321 Patent affects the inventiveness of claims 3, 7, 8, 10-13, 16, 20, 21, 23 and 24. The ISR specifically cites the columns 2 and 8-12 of the '321 Patent. (Applicant points out that EP 0 709 370 A1, also cited in the ISR, is the same disclosure as the '321 Patent.)

In response, Applicant points out that all of the subject claims require an oxo (i.e., an oxygen atom double bonded to a ring carbon) at the 1-position of the bicyclic compound. In contrast, even the most generic formula of the '321 Patent does not teach or suggest an oxo at the corresponding position (at either -W- or -Y- of the '321 Patent). Thus, the '321 does not teach, even generically, a compound that is structurally similar to any encompassed by the subject claims. For this reason alone, the '321 Patent does not affect the novelty or inventiveness of any of the subject claims.

3. Janda.

The ISR alleges that Janda affects the inventiveness of each of the subject claims.

In response, Applicant points out that Janda has absolutely no relevance to the subject invention. Specifically, the subject invention relates to the synthesis of dihydroisoquinolinone (DHQ) derivative compounds and combinatorial libraries. In contrast, Janda teaches absolutely nothing about the synthesis of such compounds or libraries. Accordingly, Janda does not, either alone or in combination, affect the inventiveness of any of the subject claims.

4. U.S. Pat. No. 5,877,278.

The ISR alleges that U.S. Pat. No. 5,877,278 (the '278 Patent) affects the inventiveness of method claims 27 to 34. The ISR specifically cites the columns 2-3, Table IX and Examples 19-23 of the '278 Patent.

In response, Applicant points out that each method claim requires the use of a 4-nitrohomophthalic acid derivative. See, for example, step (c) of claim 27, upon which claims 28 to 34 directly or indirectly depend. By contrast, the '278 Patent does not teach the use of such an acid derivative or anything remotely similar.

Moreover, the isoquinolinone derivatives taught in the '278 Patent are substituted at the 4-position. See, for example, the compounds shown in Table IX of the '278 Patent. In contrast, all the of the subject compounds and all of the compounds that result from method claims 27 to 34 are unsubstituted (i.e., have hydrogen) at the 4-position of the isoquinolinone structure. For these reasons, the '278 Patent does not affect the inventiveness of method claims 27 to 34.

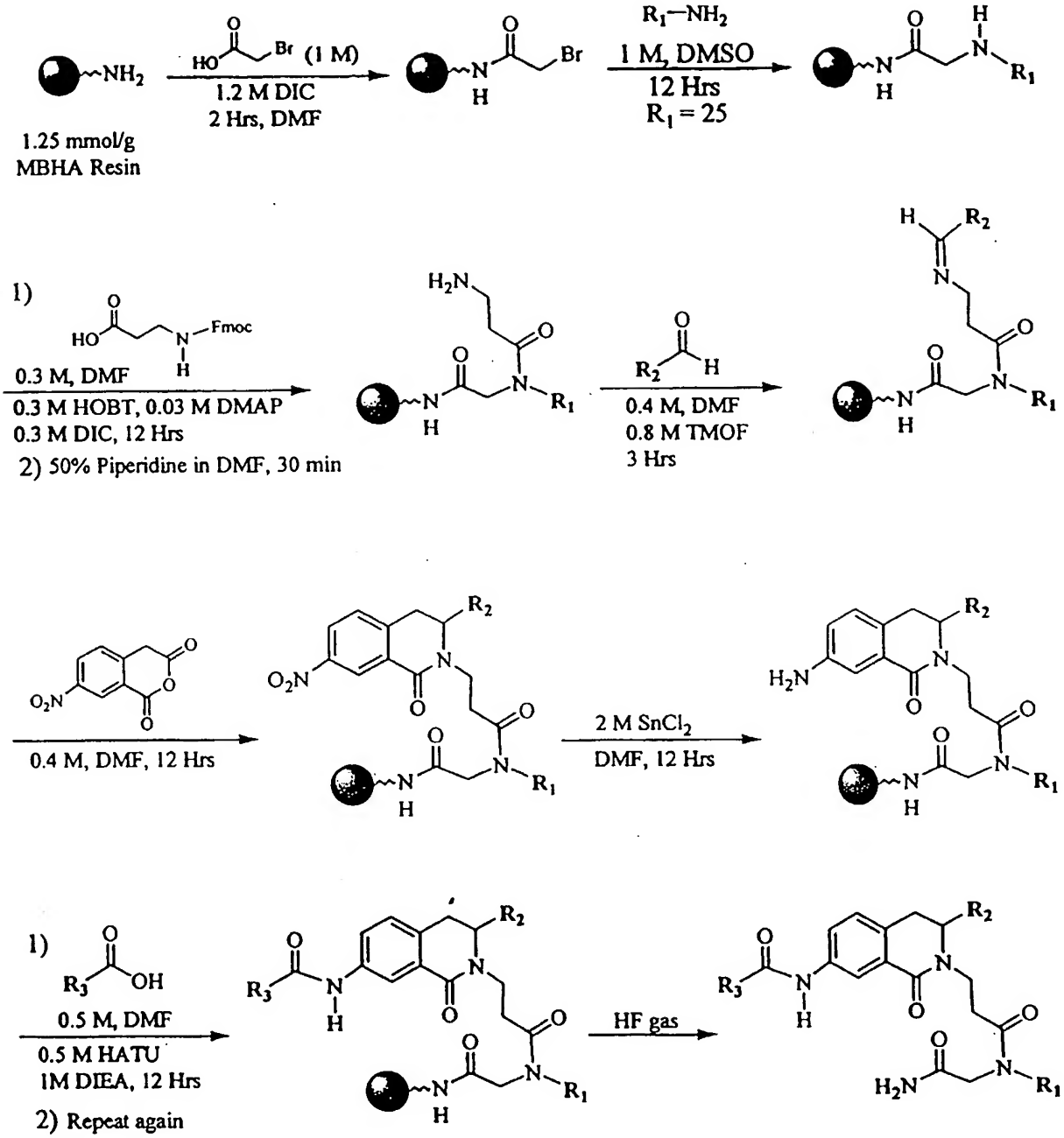

1.25 mmol/g
MBHA Resin
1.2 M DIC
2 Hrs, DMF
1 M, DMSO
12 Hrs
R_1 = 25
0.3 M, DMF
0.3 M HOBT, 0.03 M DMAP
0.3 M DIC, 12 Hrs
2) 50% Piperidine in DMF, 30 min
0.4 M, DMF
0.8 M TMOF
3 Hrs
0.4 M, DMF, 12 Hrs
2 M $SnCl_2$
DMF, 12 Hrs
0.5 M, DMF
0.5 M HATU
1M DIEA, 12 Hrs
2) Repeat again
HF gas

FIGURE 1

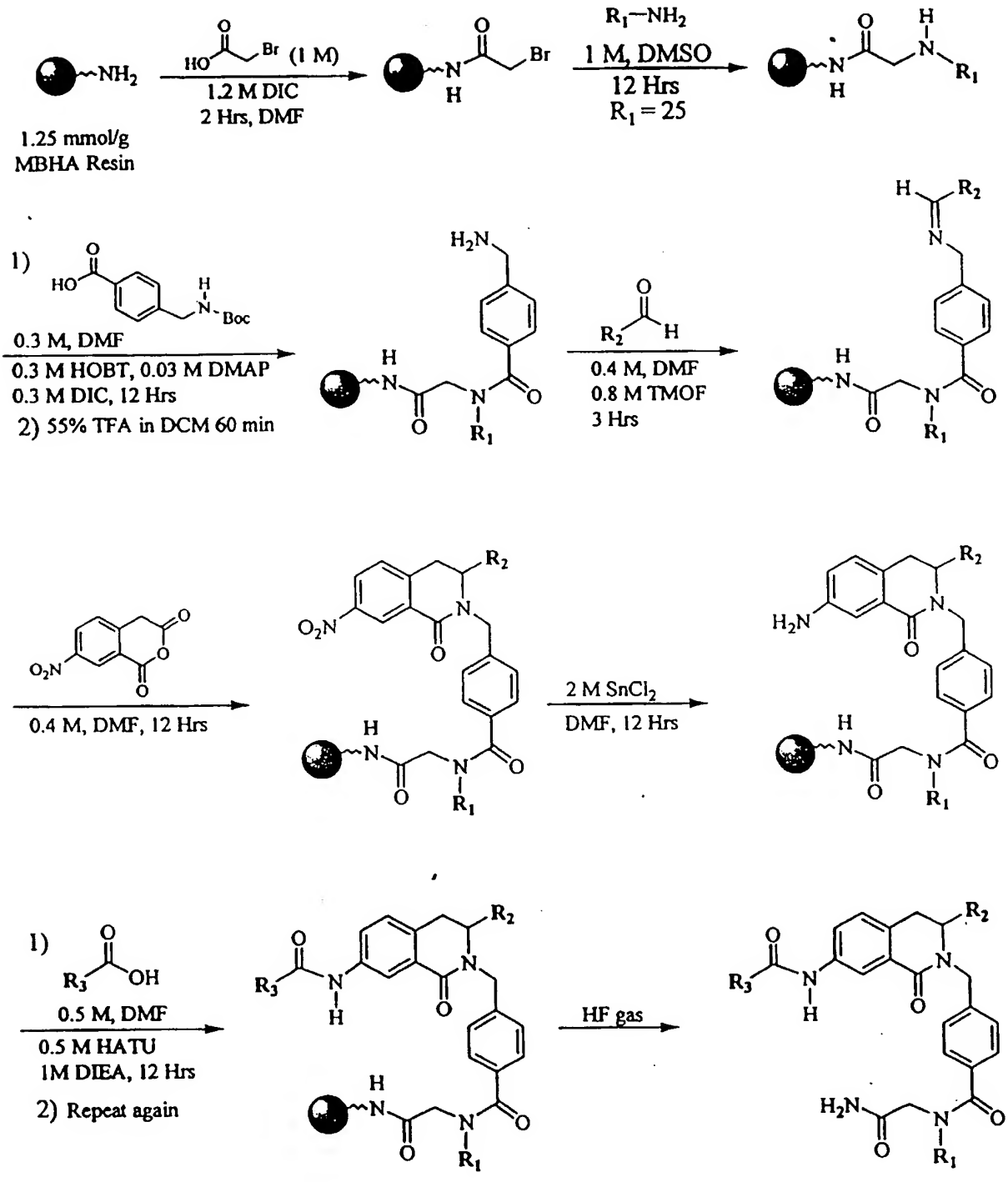

1.25 mmol/g
MBHA Resin
(1 M)
1.2 M DIC
2 Hrs, DMF
R_1—NH_2
1 M, DMSO
12 Hrs
R_1 = 25
1)
0.3 M, DMF
0.3 M HOBT, 0.03 M DMAP
0.3 M DIC, 12 Hrs
2) 55% TFA in DCM 60 min
0.4 M, DMF
0.8 M TMOF
3 Hrs
0.4 M, DMF, 12 Hrs
2 M $SnCl_2$
DMF, 12 Hrs
1)
0.5 M, DMF
0.5 M HATU
1M DIEA, 12 Hrs
2) Repeat again
HF gas

FIGURE 2

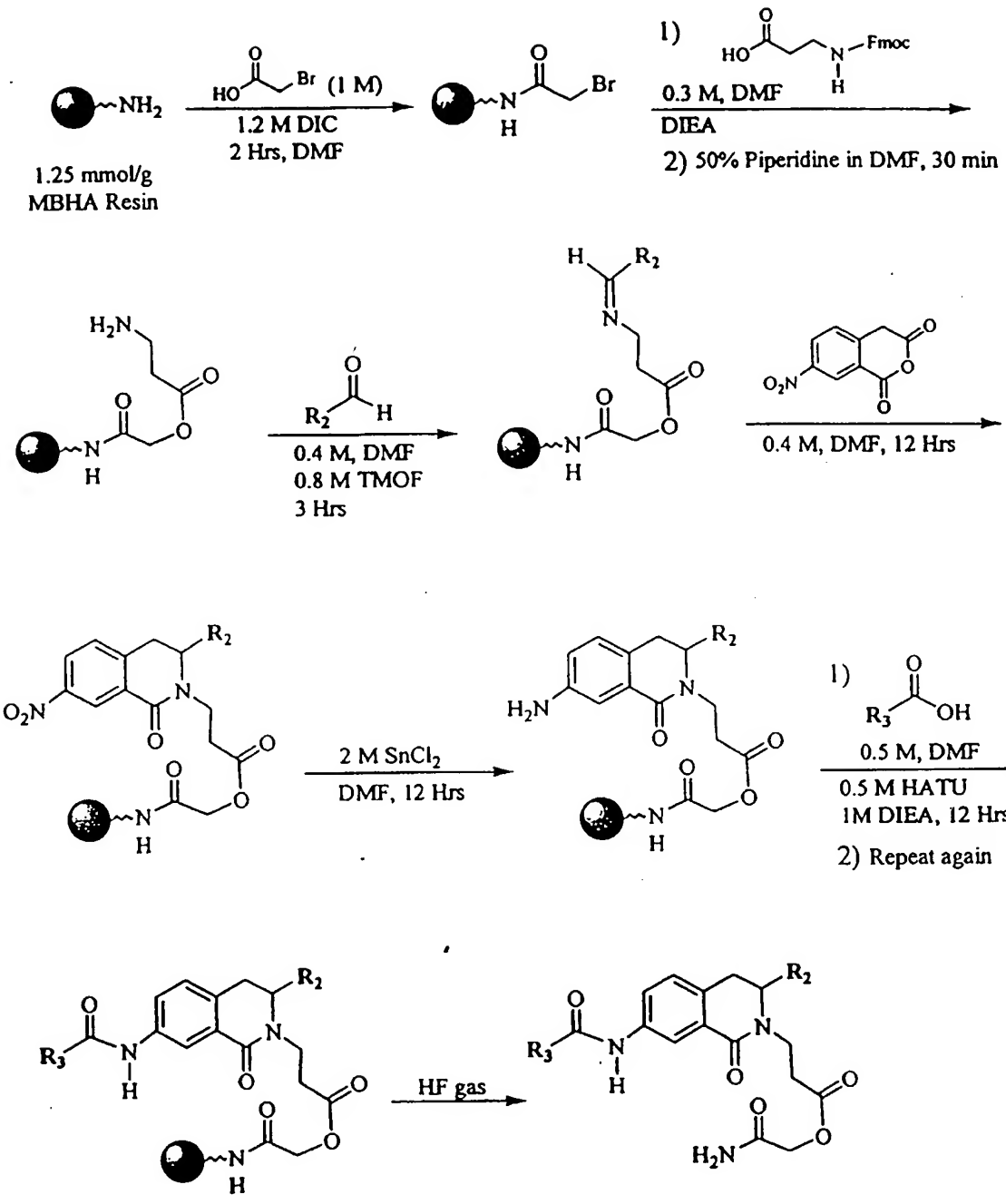

1.25 mmol/g
MBHA Resin
(1 M)
1.2 M DIC
2 Hrs, DMF
1)
0.3 M, DMF
DIEA
2) 50% Piperidine in DMF, 30 min
0.4 M, DMF
0.8 M TMOF
3 Hrs
0.4 M, DMF, 12 Hrs
2 M SnCl2
DMF, 12 Hrs
1)
0.5 M, DMF
0.5 M HATU
1M DIEA, 12 Hrs
2) Repeat again
HF gas

FIGURE 3

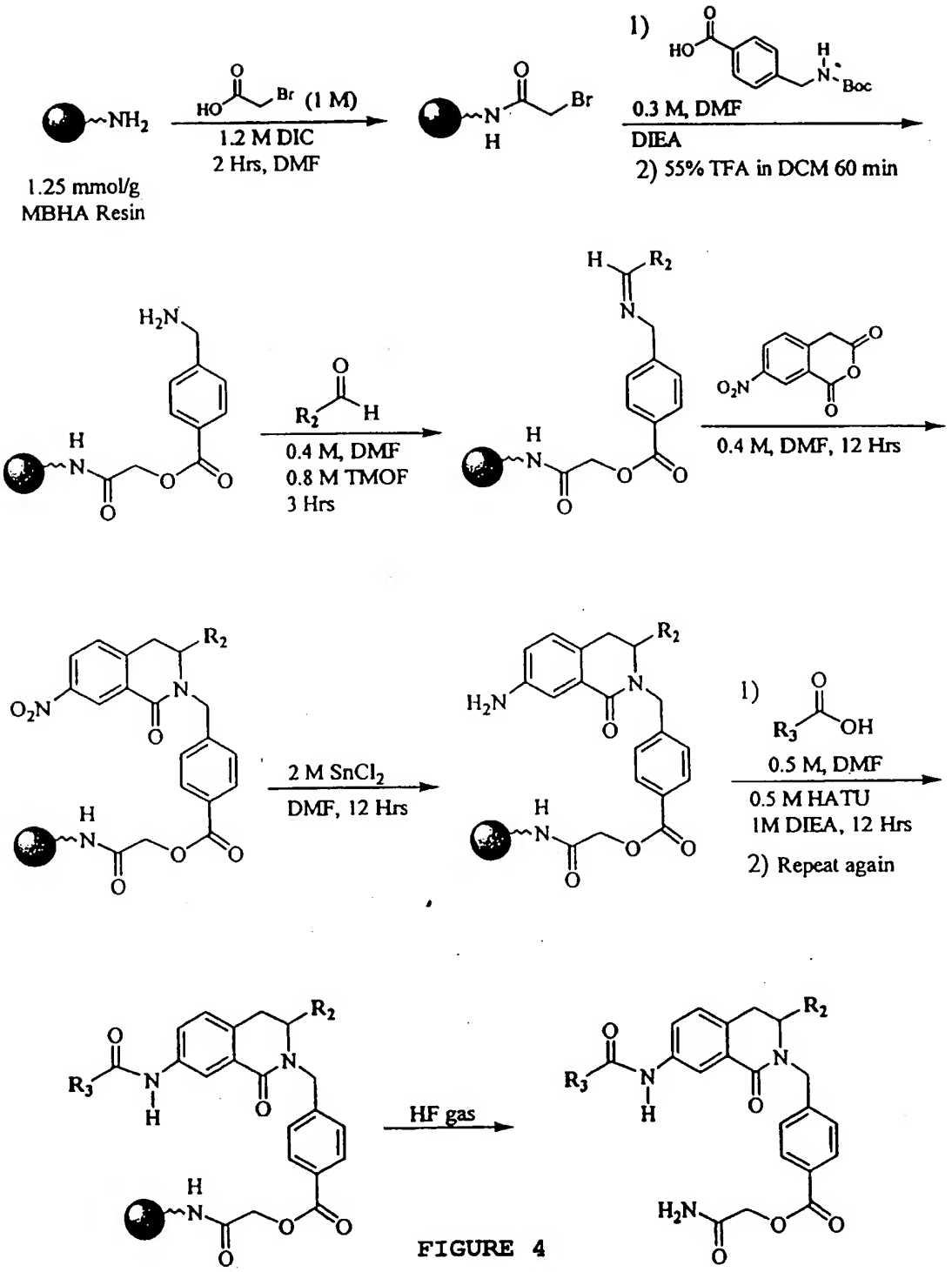

1.25 mmol/g
MBHA Resin
1.2 M DIC
2 Hrs, DMF
0.3 M, DMF
DIEA
2) 55% TFA in DCM 60 min
0.4 M, DMF
0.8 M TMOF
3 Hrs
0.4 M, DMF, 12 Hrs
2 M SnCl2
DMF, 12 Hrs
0.5 M, DMF
0.5 M HATU
1M DIEA, 12 Hrs
2) Repeat again
HF gas

FIGURE 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/20774

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 435/7.1, 7.2; 436/501, 518; 546/139, .41, 142, 146, 147, 148, 149, 150; 549/398, 399

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	US 5,602,145 A (SAMANEN) 11 February 1997, see entire document, especially Abstract, columns 1-7 and Examples 1-3.	1, 2, 4-6, 9, 14, 15, 17-19, 22 --- 3, 7, 8, 10-13, 16, 20, 21, 23-34
X --- Y	US 5,629,321 A (OKUMURA et al) 13 May 1997, see entire document, especially columns 2 and 8-12.	1, 2, 4-6, 9, 14, 15, 17-19, 22 --- 3, 7, 8, 10-13, 16, 20, 21, 23-34

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 15 OCTOBER 2000	Date of mailing of the international search report 08 NOV 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT	Authorized officer Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet) (July 1998)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/20774

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	EP 0 709 370 A1 (MITSUI TOATSU CHEMICALS, INC.) 01 May 1996 (01/05/96), see pages 1, 2 and 7-11.	1, 2, 4-6, 9, 14, 15, 17-19, 22 --- 3, 7, 8, 10-13, 16, 20, 21, 23-34
X --- Y	WO 94/29273 A1 (SMITHKLINE BEECHAM CORPORATION) 22 December 1994 (22/12/94), see Abstract and pages 3-9 and 17-19.	1, 2, 4-6, 9, 14, 15, 17-19, 22 --- 3, 7, 8, 10-13, 16, 20, 21, 23-34
Y	JANDA, K.D. Tagged versus Untagged Libraries: Methods for the Generation and Screening of Combinatorial Libraries. Proc. Natl. Acad. Sci. USA, November 1994, Vol. 19, pp. 10779-10785.	1-34
Y	US 5,877,278 A (ZUCKERMANN et al) 02 March 1999, see entire document, especially columns 2-3, Table IX and Examples 19-23 found in columns 36-54.	27-34

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/20774

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/20774

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (7):

G01N 33/53, 33/543, 33/566; C07D 217/00, 217/02, 217/06, 217/22, 311/04, 311/74, 311/76; 411/00, 413/00, 417/00, 419/00

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

435/7.1, 7.2; 436/501, 518; 546/139, 141, 142, 146, 147, 148, 149, 150; 549/398, 399

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

WEST, STN (Registry, CAPlus, USPatFull, BIOSIS, SciSearch, Medline)
Terms: Structure search, dihydroisoquinolinone, solid, suppor?, resin, bead

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s) 1-13, drawn to a combinatorial library.
Group II, claim(s) 14-26, drawn to a single compound.
Group III, claim(s) 27-34, drawn to a method of preparing a DHQ derivative.

The inventions listed as Groups I-III do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The three groups do not share a special technical feature. The technical feature that links the claims in Group I is the combinatorial library. The technical feature that links the claims of Group II are then individual compounds of specific structure. As a library is a collection of compounds (not an individual compound) these represent different inventive concepts and the groups lack unity.

Furthermore, the technical feature that links the claims in Group III is the compounds made by the method and these compounds are not the combinatorial library of Group I and need not be the individual compounds of Group II.